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(54) Title: PIPERIDINES USEFUL FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS

(57) Abstract: The invention relates to compounds which are substituted chiral or achiral derivatives of 3- or 4- aminopiperidine of the general formula (I). The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of general formula I and especially their use as inhibitors of β-secretases.

PIPERIDINES USEFUL FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS

The invention relates to substituted amino-aza-cycloalkane derivatives of the general formula I. Parts of these compounds summarized by general formula I have been described in WO 02/24649 as inhibitors of plasmepsin II, useful as antimalarial medicines. It has now surprisingly been found that a substantial number of said compounds are β-secretase inhibitors useful for prevention or treatment of diseases related to the formation and aggregation of amyloid-β-peptides (Aβ). More particularly, the compounds and compositions are useful for treating or preventing Alzheimer's disease, other age-associated dementias as well as related Aβ dependent diseases (e.g. β amyloid angiopathy, Down's syndrome or inclusion body myositis). The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of general formula I and especially their use as inhibitors of the transmembrane bound aspartic protease BACE1 or other related aspartic proteases.

Background of the invention: [1]

The World Health Organization (WHO) emphasized the importance of mental disorders in the World Health Report 2001 [2] by giving a comprehensive analysis of the world's fastest growing disease group. With increasing life expectancy and a prevalance of 5.5% of the population above 60 years of age, Alzheimer's disease (AD) has been recognized as a major social and financial burden for the coming decades [3]. A few years ago patients suffering from Alzheimer's disease had only little cause for hope to receive more effective therapies. At the present time the therapeutic situation has improved with respect to treatment of symptoms such as depression, sleeplessness or agitation but no treatment is available being able to halt progression or even cure Alzheimer's disease.

AD is a major degenerative disease of the brain, which is primarily - but not exclusively - associated with aging and presents clinically by progressive loss of memory, cognition,

reasoning, judgement, but also emotional instability that gradually leads to profound mental deterioration and death. The exact cause of AD is still unknown, but increasing evidence indicates a central role for Aβ in the pathogenesis of the disease [4-12]. A robust genetic association exists between the early-onset familial forms of AD and the abundance of Aβ in the brain. Mutations can be identified in a variety of loci including the amyloid precursor protein (APP) gene. Individuals with AD exhibit characteristic neuropathological markers such as neuritic plaques (and in β-amyloid angiopathy, deposits in cerebral blood vessels) as well as neurofibrillary tangles detected in the brain at autopsy. Aβ is a major component of neuritic plaques in AD brains and increasing evidence supports that Aβ neurotoxicity and fibrillar assembly are key pathogenic features of AD. Smaller numbers of neurotoxic lesions in a more restricted anatomical distribution are found in the brains of most aged humans who do not display clinical AD. In addition, amyloid deposits and vascular amyloid angiopathy also characterize individuals with Down's syndrome (trisomy 21), hereditary cerebral hemorrhage of the Dutch type and other neurodegenerative disorders.

Increase in brain levels of soluble or fibrillar forms of Aβ in AD might be due to overexpression of the amyloid precursor protein (APP), altered cleavage of APP to Aβ or decreased clearance of Aβ from the brain. Aβ is generated from APP which is a ubiquitously expressed type I protein with a large N-terminal domain, a single transmembrane domain and a short cytoplasmic domain coded by a gene located on human chromosome 21 (Price et al., Annu Rev Neurosci 21: 479-505, 1998; Selkoe, Trends Cell Biol 8: 447-453, 1998). APP can undergo several proteolytic events near and within its membrane domain.

A proteolytic activity named β-secretase initially cleaves APP to form two products: a secreted peptide named APPsβ and the membrane bound C99 fragment of APP. C99 is the substrate of a second proteolytic activity called γ-secretase, which cleaves at position 711 (40) or 713 (42) to form $A\beta_{1-40}$ and $A\beta_{1-42}$. In an alternative, non-amyloidogenic processing pathway, cleavage of APP by α-secretase within the amyloid domain results in the release of the large soluble fragment, APPsα, and generation of a 10kDa membrane anchored C-terminal fragment, C83. It can be argued that a gradual and chronic imbalance between production and clearance of Aβ proteins leads to a slow rise in its steady-state levels in the

brain tissue, resulting in Aβ accumulation and subsequently in plaque formation as well as complex molecular and cellular changes in the brain. It has also become increasingly clear that all the hereditary familial forms of AD currently known alter either the metabolism or the generation of Aβ [13 - 15].

The integrated functions of APP and its fragments in normal situations remain largely unknown. The processing of APP is similar to that of other proteins that undergo regulated intramembrane proteolysis such as Notch (Niwa et al., Cell 99: 691-702, 1999; Mumm et al., Dev Biol 228: 151-165, 2000) to generate fragments which play a role as transcription factors. Aβ naturally arises in the endoplasmatic reticulum, the Golgi apparatus or the endosomal-lysosomal system and most is secreted as Aβ 1-40 or Aβ 1-42 (5-10%). However, intracellular aggregates of Aβ also accumulate in brains of AD patients, Down's syndrome patients and aging monkeys. This precedes the appearance of neurofibrillary tangles and senile plaques in the hippocampus and entorhinal cortex of affected individuals.

In 1999 the identification of β-site APP cleaving enzyme (BACE1), also called memapsin-2 or Asp2, was described by using different approaches [16-18]. BACE1 is a membrane-bound aspartic protease with all the known functional properties and characteristics of β-secretase. It is a 501 amino acid sequence peptide most closely related to the pepsin aspartic protease family. Two aspartic protease active-site motifs with the sequence DTGS (residues 93-96) and DSGT (289-292) are present, mutation of either aspartic acid abolishes the catalytic acitivity of the enzyme. BACE1 has a single predicted C-terminal transmembrane domain (455-480) with a luminal active site. This is the correct topological orientation for APP cleavage. Six cysteins are present in the catalytic domain to form three intramolecular disulfide bonds. The number of dislufide bridges is identical to other aspartic proteases such as pepsin. While the bond spanning between Cys330-380 appears conserved, the positions of two cysteine bridges (Cys278-443, Cys 216-420) are quite different when compared to pepsin, without changing the shape of the catalytic domain. Most cell types produce Aβ, indicating broad expression of β-secretase. However, considerably more Aβ is generated in primary brain cultures than in peripheral cells (Seubert et al., Nature 361:260-3, 1993) and neurons display more β-secretase activity than astrocytes (Zhao et al., J Biol Chem

271:31407-11, 1996). The expression of BACE1 is highest in pancreas and brain, and significantly lower in most other tissues. The high expression level in pancreas can be attributed to a catalytically inactive splice variant of BACE1, lacking part of exon 3. β-secretase activity has been found in several cellular compartments including endosomes, lysosomes, Golgi and endoplasmic reticulum. Parallel to BACE1, a second homologous aspartyl protease named BACE2 was found to have β-secretase activity in vitro and is expressed at low levels in most peripheral organs, although not significantly in the brain.

Down-regulation of BACE1 protein expression with antisense oligonucleotides suppresses APPsβ production in cells transfected with APPsw[2]. On the other hand, overexpression of BACE1 in cells leads to an increase of β–secretase activity: levels of C99 and APPsβ are increased several-fold compared to untransfected cells. In mice, expressing huBACE1 in addition to human APP wild-type or carrying the Swedish mutation, the induction of APP processing results in increased brain levels of β-amyloid peptides $A\beta_{1-40}$ and $A\beta_{1-42}$ at steady state. BACE knock-out mice are fully viable. Aβ production is significantly decreased in the brain of these animals, even when the BACE null mutation is introduced in transgenic mice overexpressing APP (Luo et al., Nature Neurosci. 4:231-232, 2001). However, no deleterious side-effects due to the loss of BACE1 function was observed in these animals. The healthy phenotype of BACE1 knockouts gives β-secretase significant therapeutic potential although, as with γ-secretase, substrates other than APP may exist. The positive results from the knockout mice suggest that a potential mechanism-based toxicity might not be a major issue for BACE1 specific inhibitors.

Prior Art:

Today, at least according to our knowledge, no low-molecular-weight non-peptide, non-substrate related BACE1-inhibitor is published in the scientific literature. In the patent literature only a few documents dealing with low-molecular weight non-peptide compounds have been found by database searches (**Takeda Chemical Industries**: WO 01/87293A1 and WO 00/187293; **Vertex Pharmaceuticals**: WO 02/088101; **Elan Pharmaceuticals**: WO 02/076440 [claiming renin inhibitors from WO 97/09311 to F. Hoffmann-LaRoche, as BACE-inhibitors] or WO 03/043987 and WO 03/000261 [claiming HIV-1 protease inhibitors from US 5,846,978 to Merck & Co. as BACE-inhibitors]). Several patents dealing with peptidomimetic BACE1 inhibitors have been published so far (**Elan Pharmaceuticals**: WO 00/77030; WO 01/70672; WO 02/02520; WO 02/02512; WO 02/02506, WO 02/02505; WO 02/085877; WO 02/094768; WO 02/100399; WO 02/100856; WO 02/100820; WO 03/002122; WO 03/006453; WO 03/006423; WO 03/006021; WO 03/006013; WO 03/037325; WO 03/030886; WO 03/040096; WO 03/039454; US 6,552,013; 03/45378; WO 03/47576; WO 03/43975; WO 03/43618; **Pfizer Products Inc.**: EP 1233021; **Neurologic Inc.**: WO 02/096897; US 6,562,783; **Sumitomo Pharmaceutical Co Ltd.**: JP 14173448; **Oklahoma Medical Research Foundation**: WO 02/053594; WO 01/00665; **GlaxoSmithKline**: WO-03/45913; WO 03/45903).

No reports or publications were found about pre-clinical or even clinical investigations with compounds contemplated in the patents listed above.

The present invention relates to the identification of novel as well as partially structurally known, low molecular weight non-peptidic inhibitors of BACE1 of the **general formula I** (exhibiting a different binding mode to the protein compared to substrate derived inhibitors) to treat and/or prevent Alzheimer's Disease and other CNS-disorders associated with amyloid deposition in the brain.

The compounds of general formula I were tested against BACE1, plasmepsin II, plasmepsin IV, human cathepsin D, human cathepsin E, human renin and HIV-protease.

Assay conditions to determine inhibition of BACE1 activity:

The proteolytic activity of human BACE1 (Sinha, S., et al. (1999), Nature 402:537-540) was determined in a FRET-based assay, with a peptide-substrate whose sequence corresponds to the cleavage site of β-secretase in the Swedish variant of the amyloid precursor protein.
Commercial source of the BACE1-assay:
PanVera Corporation
Madison WI 53719 USA
(www.panvera.com)

Descriptions of the assays against the other aspartic proteases can be found in WO 02/24649 and WO 02/38534.

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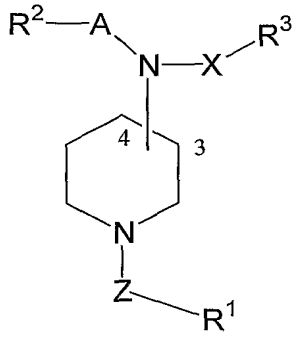
The present invention relates to pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders comprising substituted piperidines of the **general formula I**, wherein the substituent is attached either to position 3 or position 4 of the central piperidine-ring:



General Formula I

wherein

$\mathbf{R^1}$ represents lower alkyl; lower alkenyl-lower alkyl; lower alkynyl-lower alkyl; cycloalkyl; cycloalkenyl-lower alkyl; heterocyclyl; aryl; heteroaryl;

$\mathbf{R^2}$ represents cycloalkyl; cycloalkenyl; heterocyclyl; aryl; heteroaryl;

$\mathbf{R^3}$ represents lower alkyl; cycloalkyl; cycloalkenyl; heterocyclyl; aryl; heteroaryl;

A represents $-(CH_2)_m-$;

X represents $-(CH_2)_n-CH_2-(CH_2)_j-$; $-(C=O)-(CH_2)_p-$; $-(C=O)-(CH_2)_p-NH-(CH_2)_q-$; $-(C=O)-(CH_2)_f-O-(CH_2)_p-$; $-(C=O)-(CH=CH)-$; $-(SO_2)-(CH_2)_p-$; $-(SO_2)-NH-(CH_2)_p-$; $-(SO_2)-(CH=CH)-$;

Z represents a bond; $-((CH_2)_n-CH_2-(CH_2)_j)-$; $-((CH_2)-(CH=CH))-$; $-(CH_2)_g-NH-(CO)-$; $-(CH_2)_g-NH-(CO)-O-$; $-(CH_2)_g-NH-(CO)-NH-$; $-(CH_2)_g-O-(CH_2)_m-$;

n and **j** represent the whole numbers 0, 1 or 2 and may be the same or different;

m represents the whole numbers 1, 2 or 3;

k, p and **q** represent the whole numbers 0, 1, 2, 3 or 4 and may be the same or different;

f represents the whole numbers 1, 2, 3 or 4;

g represents the whole numbers 2,3 or 4;

pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, the meso-form, pharmaceutically acceptable salts thereof, and inert carrier material.

In the definitions of the **general formula I** – if not otherwise stated – the expression lower means straight and branched chain groups with one to seven carbon atoms, preferably 1 to 4 carbon atoms which may optionally be substituted with hydroxy or lower alkoxy. Examples of lower alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec.-butyl, tert.-butyl, n-pentyl, n-hexyl, n-heptyl and the like. Examples of lower alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy; iso-butoxy, sec.-butoxy and tert.-butoxy and the like. Examples of lower alkynyl groups are ethinyl, propynyl, butynyl, pentynyl, hexynyl and the like which may be optionally substituted by hydroxy or lower alkoxy. Examples of lower alkynyloxy groups are 3-methoxy-prop-1-ynyl and the like. Lower alkylendioxy-groups as substituents of aromatic rings onto two adjacent carbon atoms are preferably methylen-dioxy and ethylen-dioxy. Lower alkylen-oxy groups as substituents of aromatic rings onto two adjacent carbon atoms are preferably ethylen-oxy and propylen-oxy. Examples of lower alkanoyl-groups are acetyl, n-propanoyl and n-butanoyl.

The expression **cycloalkyl**, alone or in combination, means a saturated cyclic hydrocarbon ring system with 3 to 6 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl and

cyclohexyl which may be mono- or di- substituted with lower alkyl; lower alkoxy; aryl-lower alkoxy; heteroaryl-lower alkoxy; aryl-lower alkyl-amino; heteroaryl-lower alkyl-amino; lower alkyl-amino; bis-(lower alkyl)-amino; aryl-lower alkoxy-lower alkyl; heteroaryl-lower alkoxy-lower alkyl; aryl-lower alkyl-amino-lower alkyl; heteroaryl-lower alkyl-amino-lower alkyl; aryl-sulfonyl-amino-lower alkyl; heteroaryl-sulfonyl-amino-lower alkyl; cycloalkyl-sulfonyl-amino-lower alkyl; heterocyclyl-sulfonylamino-lower alkyl; aryl-lower alkyl-sulfonyl-amino-lower alkyl; heteroaryl-lower alkyl-sulfonyl-amino-lower alkyl; cycloalkyl-lower alkyl-sulfonyl-amino-lower alkyl; heterocyclyl-lower alkyl-sulfonylamino-lower alkyl; lower alkyl-sulfonyl-amino-lower alkyl; aryl amino-carbonyl-lower alkyl; heteroaryl-amino-carbonyl-lower alkyl; cycloalkyl-amino-carbonyl-lower alkyl; heterocyclyl-amino-carbonyl-lower alkyl; lower alkyl-amino-carbonyl-lower alkyl; aryl-ureido-lower alkyl; heteroaryl-ureido-lower alkyl; cycloalkyl-ureido-lower alkyl; lower alkyl-ureido-lower alkyl; aryl-lower alkyl-ureido-lower alkyl and in case the substituent on the **cycloalkyl** contains aryl- or heteroaryl-units those may again be mono-, di or tri-substituted with substituents as outlined herein before.

The expression **cycloalkenyl**, alone or in combination, means an unsaturated cyclic hydrocarbon ring system with 5 to 7 carbon atoms, e.g. cyclopentenyl, cyclohexenyl and cycloheptenyl which may be substituted with lower alkyl groups or lower alkoxy groups.

The expression **heterocyclyl**, alone or in combination, means a saturated or unsaturated (but not aromatic) five-, six- or seven-membered ring containing one or two heteroatoms chosen from nitrogen, oxygen or sulfur which may be the same or different and which rings may be substituted with lower alkyl; lower alkenyl; aryl; heteroaryl; aryl-lower alkoxy; aryl-lower alkoxy-lower alkyl; aryl-oxy; heteroaryl-lower alkoxy; heteroaryl-lower alkoxy-lower alkyl; heteroaryl-oxy; amino; bis-(lower alkyl)-amino; alkanoyl-amino; halogen; hydroxy; hydroxy-lower alkyl; lower alkoxy; phenoxy. Examples of such rings are morpholinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, 1,4-dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dihydropyrrolyl, imidazolidinyl, dihydropyrazolyl, pyrazolidinyl, dihydroquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl and the like, and substituted derivatives of such type rings with substituents as outlined hereinbefore.

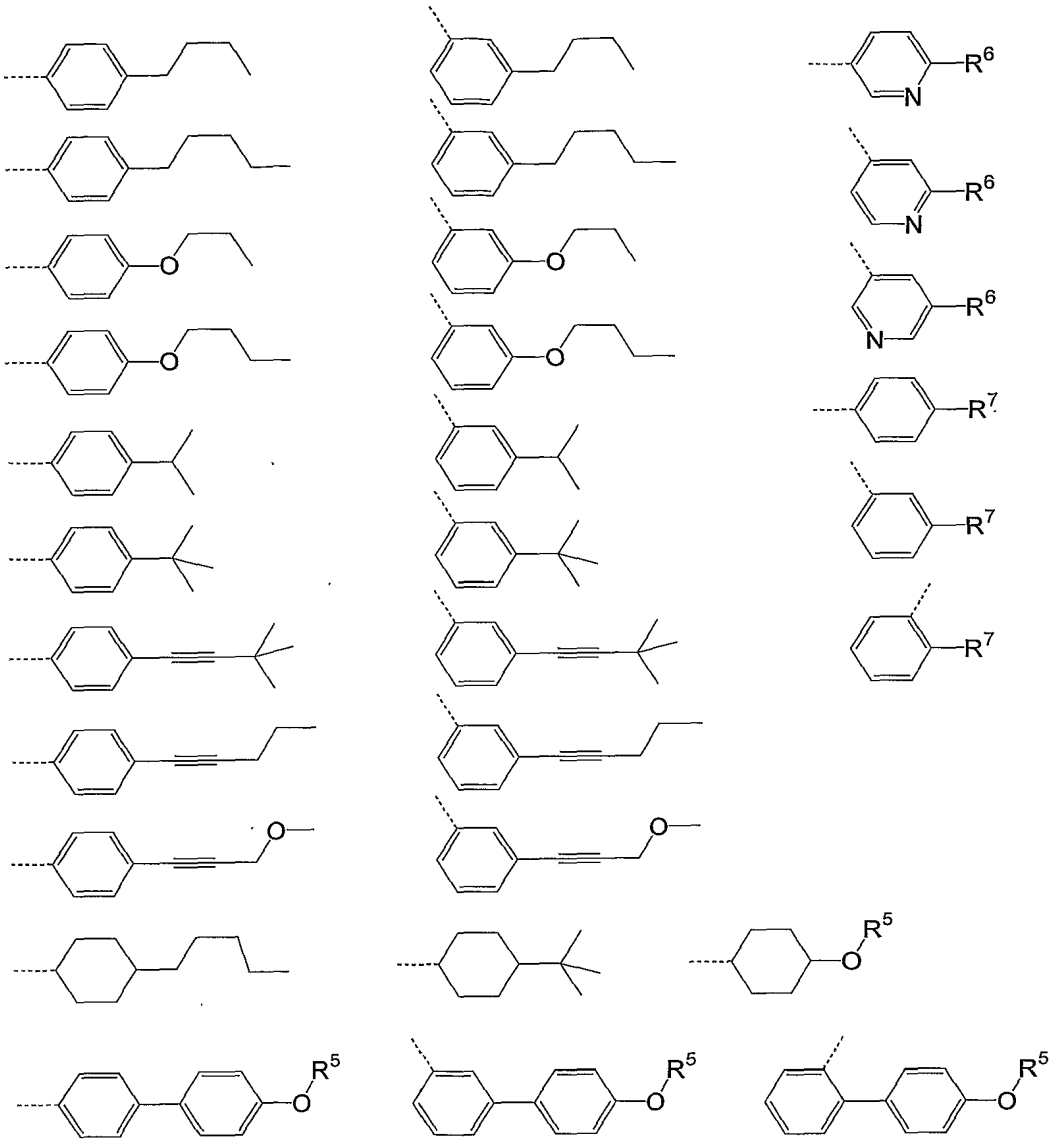
The expression **heteroaryl**, alone or in combination, means six-membered aromatic rings containing one to four nitrogen atoms; benzofused six-membered aromatic rings containing one to three nitrogen atoms; five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom and benzo-fused derivatives thereof; five-membred aromatic rings containing two nitrogen atoms and benzo-fused derivatives thereof; five membered aromatic rings containig one oxygen and one nitrogen atom and benzo-fused derivatives thereof; five membred aromatic rings containing one sulfur and one nitrogen atom and benzo fused derivatives thereof; five membered aromatic rings containing three nitrogen atoms and benzo fused derivatives thereof or the tetrazolyl ring; examples of such rings are furanyl, thienyl, pyrrolyl, pyridinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazinyl, pyrazolyl, pyridazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, and the like, whereby such ring systems may be mono-, di- or tri-substituted with heterocyclyl; heterocyclyl-lower alkyl-amino; cycloalkyl; cycloalkyl-amino; cycloalkyl-lower alkyl-amino; aryl; heteroaryl; aryloxy; aryl-lower alkoxy; heteroaryl-lower alkoxy; aryl-lower alkyl-amino; heteroaryl-lower alkyl-amino; lower alkyl; lower alkenyl; lower alkynyl; lower alkyl-carbonyl; amino; lower alkyl-amino; aryl-amino; heteroaryl-amino; bis-(lower-alkyl)-amino; bis-aryl-amino; (aryl)(heteroaryl)-amino; lower alkanoyl-amino; aryl-carbonyl-amino; heteroaryl-carbonyl-amino; lower alkyl-sulfonyl-amino; aryl-sulfonyl-amino; heteroaryl-sulfonyl-amino; aryl-lower alkyl-sulfonyl-amino; heteroaryl-lower alkyl-sulfonyl-amino; ω-amino-lower alkyl; halogen; hydroxy; carboxyl; lower alkoxy-carbonyl; lower alkoxy; vinyloxy; allyloxy; ω-hydroxy-lower alkyl; cyano; amidino; trifluoromethyl; lower alkyl-sulfonyl and the like and in case the substituent on the **heteroaryl** contains aryl or heteroaryl, those units may again be mono-, di- or tri-substituted with substituents as outlined herein before.

The expression **aryl**, alone or in combination, means six membered aromatic rings and condensed systems like naphthyl or indenyl and the like, whereby such ring systems may be mono-, di- or tri-substituted with cycloalkyl; heterocyclyl; aryl; heteroaryl; aryloxy; aryl-lower alkoxy; heteroaryl-lower alkoxy; lower alkyl; lower alkenyl; lower alkynyl; lower alkenylen; lower alkyl-carbonyl; aryl-carbonyl; heteroaryl-carbonyl; cycloalkyl-carbonyl; heterocyclyl-carbonyl; amino; lower alkyl-amino; aryl-amino; heteroaryl-amino; bis-(lower-

alkyl)-amino; bis-aryl-amino; lower alkanoyl-amino; aryl-carbonyl-amino; heteroaryl-carbonyl-amino; lower alkyl-sulfonyl-amino; cycloalkyl-sulfonyl-amino; cycloalkyl-lower alkyl-sulfonyl-amino; aryl-sulfonyl-amino; heteroaryl-sulfonyl-amino; aryl-lower alkyl-sulfonyl-amino; ω-amino-lower alkyl; halogen; hydroxy; carboxyl; lower alkoxy-carbonyl; lower alkoxy; vinyloxy; allyloxy; ω-hydroxy-lower alkyl; ω-hydroxy-lower alkoxy; cyano; amidino; trifluoromethyl; lower alkyl-sulfonyl and the like and in case the substituent on the **aryl** contains aryl or heteroaryl, those units may again be mono-, di- or tri-substituted with substituents as outlined herein before.

The expression halogen means fluorine; chlorine; bromine and iodine but fluorine, chlorine and bromine are preferred.

In addition to the definitions given above for substituents $\mathbf{R^2}$ and $\mathbf{R^3}$, the following structural formulae represent structural moieties for substituents $\mathbf{R^2}$ and $\mathbf{R^3}$ of special interest and are a preferred aspect of the invention:


R6
N
R6
N
R6
N
R7
R7
R7
O
O
O
O
O
O
R5
O
R5
O
R5
O

wherein

R^5 represents lower alkyl; hydroxy-lower alkyl; aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; heterocyclyl; heterocyclyl-lower alkyl; cycloalkyl; cycloalkyl-lower alkyl;

R^6 represents lower alkyl; lower alkynyl; aryl; heteroaryl; heterocyclyl; aryl-amino; heteroaryl-amino; cycloalkyl-amino; aryl-lower alkyl-amino; heteroaryl-lower alkyl-amino; heterocyclyl-lower alkyl-amino; cycloalkyl-lower alkyl amino; aryloxy; heteroaryloxy; cyloalkyloxy; aryl-lower alkyloxy; heteroaryl-lower alkyloxy; heterocyclyl-lower alkyloxy; cycloalkyl-lower alkyloxy;

R^7 represents aryl; heteroaryl; heterocyclyl; cycloalkyl; aryl-amino; heteroaryl-amino; cycloalkyl-amino; aryl-lower alkyl-amino; heteroaryl-lower alkyl-amino; heterocyclyl-lower alkyl-amino; cycloalkyl-lower alkyl amino; aryl-oxy; heteroaryl-oxy; aryl-lower alkyl-oxy; heteroaryl-lower alkyl-oxy;

It is understood that the substituents outlined relative to the expressions cycloalkyl, heterocyclyl, heteroaryl and aryl have been omitted in the definitions of the formulae I to XI and in claims 1 to 15 for clarity reasons but the definitions in formulae I to XI and in claims 1 to 15 should be read as if they are included therein.

The expression pharmaceutically acceptable salts encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, methylsulfonic acid, p-toluolsulfonic acid and the like or in case the compound of formula I is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like.

The compounds of general formula I can be transformed to suitable prodrugs like carboxylic acid esters, phosphonic acid esters, sulfuric acid esters, acetales, ketales, phenyl carbamates, amino acid amides, *Mannich* bases, *Schiff* bases, oximes, enolesters, oxazolidines,

thiazolidines and the like if necessary and advantageous. All forms of prodrugs leading to an active component comprised in general formula I are included in the present invention.

The compounds of the general formula I can contain one or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates and mixtures of diastereomeric racemates and the meso-form. The compounds of general formula I may also contain one or more partially or fully substituted carbon-carbon double bond(s), which may be Z- or E-substituted.
The present invention encompasses all these forms. Mixtures may be separated in a manner known per se, i.e. by column chromatography, thin layer chromatography, HPLC, crystallization and the like.

The compounds of the general formula I and their pharmaceutically acceptable salts may be used as therapeutics e.g. in form of pharmaceutical compositions. They may especially be used in prevention or treatment of CNS-disorders related to amyloid-β-peptide-deposition in the brain, like Alzheimer's disease, Down's Syndrome, Inclusion Body Myositis and other age-associated dementias as well as other amyloid-β-peptide-dependent diseases. These compositions may be administered in enteral or oral form e.g. as tablets, dragees, gelatine capsules, emulsions, solutions or suspensions, in nasal form like sprays or rectally in form of suppositories. These compounds may also be administered in intramuscular, parenteral or intraveneous form, e.g. in form of injectable solutions.

These pharmaceutical compositions may contain the compounds of general formula I as well as their pharmaceutically acceptable salts in combination with inorganic and/or organic excipients which are usual in the pharmaceutical industry like lactose, maize or derivatives thereof, talcum, stearinic acid or salts of these materials.

For gelatine capsules vegetable oils, waxes, fats, liquid or half-liquid polyols and the like may be used. For the preparation of solutions and sirups e.g. water, polyols saccharose, glucose and the like are used. Injectables are prepared by using e.g. water, polyols, alcohols,

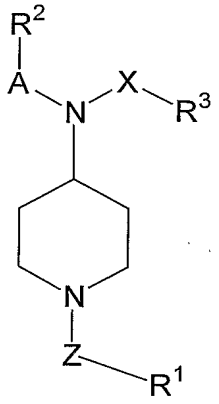
glycerin, vegetable oils, lecithin, liposomes and the like. Suppositories are prepared by using natural or hydrogenated oils, waxes, fatty acids (fats), liquid or half-liquid polyols and the like.

The compositions may contain in addition preservatives, stability improving substances, viscosity improving or regulating substances, solubility improving substances, sweeteners, dyes, taste improving compounds, salts to change the osmotic pressure, buffer, anti-oxidants and the like.

The compounds of general formula I may also be used in combination with one or more other therapeutically useful substances e. g. with other medicaments used for the treatment of symptoms of Alzheimer's disease such as acetylcholine esterase inhibitors, medicaments for the treatment of depression, agitation or sleeplessness, with other medicaments/substances which halt or retard the formation of amyloid-plaques in the brain such as other BACE1-inhibitors or γ-secretase-inhibitors, with antioxidants such as vitamin E, with LDL lowering agents such as HMG-CoA-reductase inhibitors and the like.

The dosage may vary within wide limits but should be adapted to the specific situation. In general the dosage given in oral form should daily be between about 1 mg and about 3 g, preferably between about 10 mg and about 1 g, especially preferred between 5 mg and 300 mg, per adult with a body weight of about 70 kg. The dosage should be administered preferably in 1 to 3 doses per day, which are of equal weight. As usual, children should receive lower doses which are adapted to body weight and age.

A group of preferred compounds for incorporation into pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders are compounds of the **formula II**:



Formula II

wherein

R^1, R^2, R^3, X, Z and **A** are as defined in **general formula I** above

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

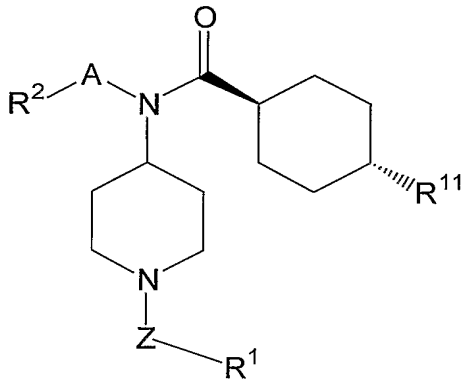
A group of especially preferred compounds according to **formula II** for incorporation into pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders are compounds wherein **R^1, R^2, R^3, Z** and **A** are as defined in **general formula I** above and wherein **X** represents $-((C=O)-NH-(CH_2)_q)-$ and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

A group of especially preferred compounds according to **formula II** for incorporation into pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders are compounds wherein **R^1, R^2, R^3, Z** and **A** are as defined in **general formula I** above and wherein **X** represents $-((C=O)-(CH_2)_q)-$ and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric

racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

Another group of preferred compounds for incorporation into pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders are compounds of the **formula III**:

Formula III



wherein

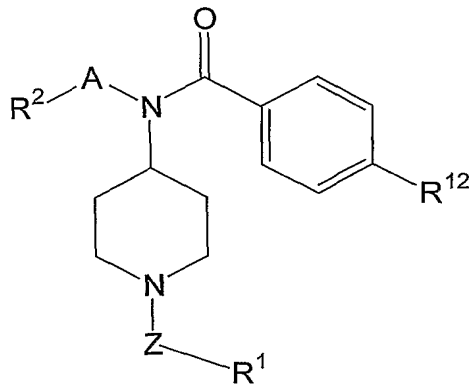
R^1, R^2, Z and **A** are as defined in **general formula I** above

R^{11} represents lower alkyl; lower alkyloxy; cycloalkyl; cycloalkyl-lower alkyloxy;

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

Another group of preferred compounds for incorporation into pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders are compounds of the **formula IV**:

Formula IV



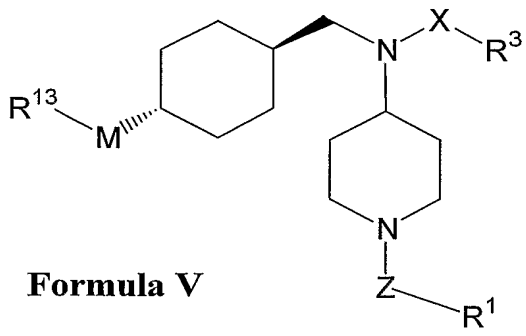
wherein

R^1, R^2 **A** and **Z** are as defined in **general formula I** above, and wherein

R^{12} represents lower alkyl; lower alkyloxy; lower alkyloxy-lower alkyloxy; aryl; heteroaryl; heterocyclyl;

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

Another group of preferred compounds for incorporation into pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders are compounds of the **formula V**:



Formula V

wherein

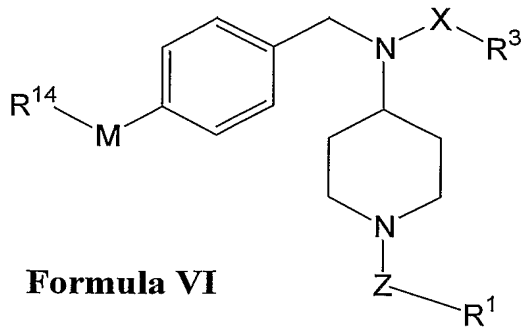
R^1, R^3, X and **Z** are as defined in **general formula I** above and

M represents -O-; -CH_2-;

R^{13} represents hydrogen; lower alkyl; lower alkenyl; lower alkynyl; cycloalkyl; cycloalkyl-lower alkyl; aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl;

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

Another group of preferred compounds for incorporation into pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders are compounds of the **formula VI**:



Formula VI

wherein

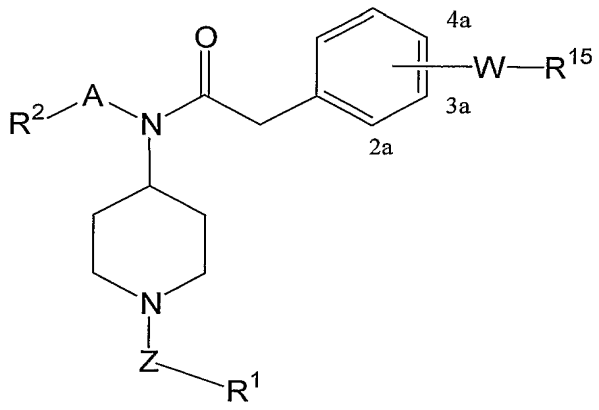
R^1, R^3, X, and **Z** are as defined in **general formula I**

M represents -O-; -CH_2-; or can be absent;

R^{14} represents hydrogen; lower alkyl; aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; cycloalkyl; cycloalkyl-lower alkyl; and in case **M** is absent, **R^{14}** can also represent heterocyclyl;

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

Another group of preferred compounds for incorporation into pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders are compounds of the **formula VII**:



Formula VII

wherein

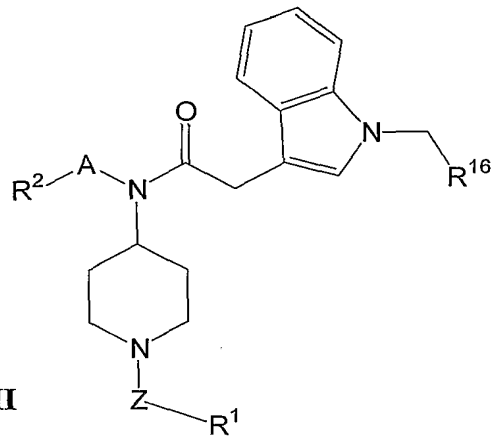
R^1, R^2, A and **Z** are as defined in **general formula I** above

R^{15} represents hydrogen; lower alkyl; lower alkenyl; lower alkynyl; cycloalkyl; cycloalkyl-lower alkyl; aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; and in case **W** represents a bond, **R^{15}** can also represent heterocyclyl; cyano; trifluoromethyl; trifluoromethoxy;

W represents a bond; -O-; -NH-; -N(R^{11})-; whereby in the group -N(R^{11})- the substituent **R^{11}** is as defined in formula III above, and **W** may be attached to the benzene-ring either in position 2a or 3a or 4a;

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

Another group of preferred compounds for incorporation into pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders are compounds of the **formula VIII**:



Formula VIII

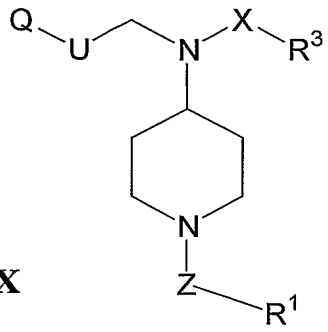
wherein

R^1, R^2, A and Z are as defined in **general formula I** above;

R^{16} represents lower alkyl; lower alkenyl; lower alkynyl; cycloalkyl; cycloalkyl-lower alkyl; aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; heterocyclyl-lower alkyl;

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

Another group of preferred compounds for incorporation into pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders are compounds of the **formula IX**:



Formula IX

wherein

R^1, R^3, **X** and **Z** are as defined in **general formula I** above;

U represents aryl; heteroaryl;

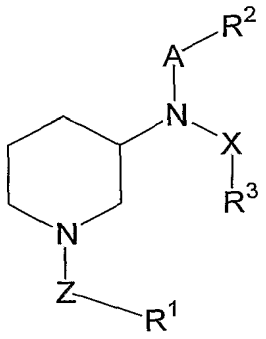
Q represents aryl; heteroaryl; cycloalkyl; heterocyclyl; alkynyl;

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

The compounds of the formulae **II** to **IX** are incorporated into pharmaceutical compositions for the treatment, prevention or delaying the onset of central nervous system disorders together with inert carrier material.

The invention also relates to novel compounds of the **formula XI**:

Formula XI



wherein

R^1, R^2, R^3, **X**, **Z** and **A** are as defined in **general formula I** above

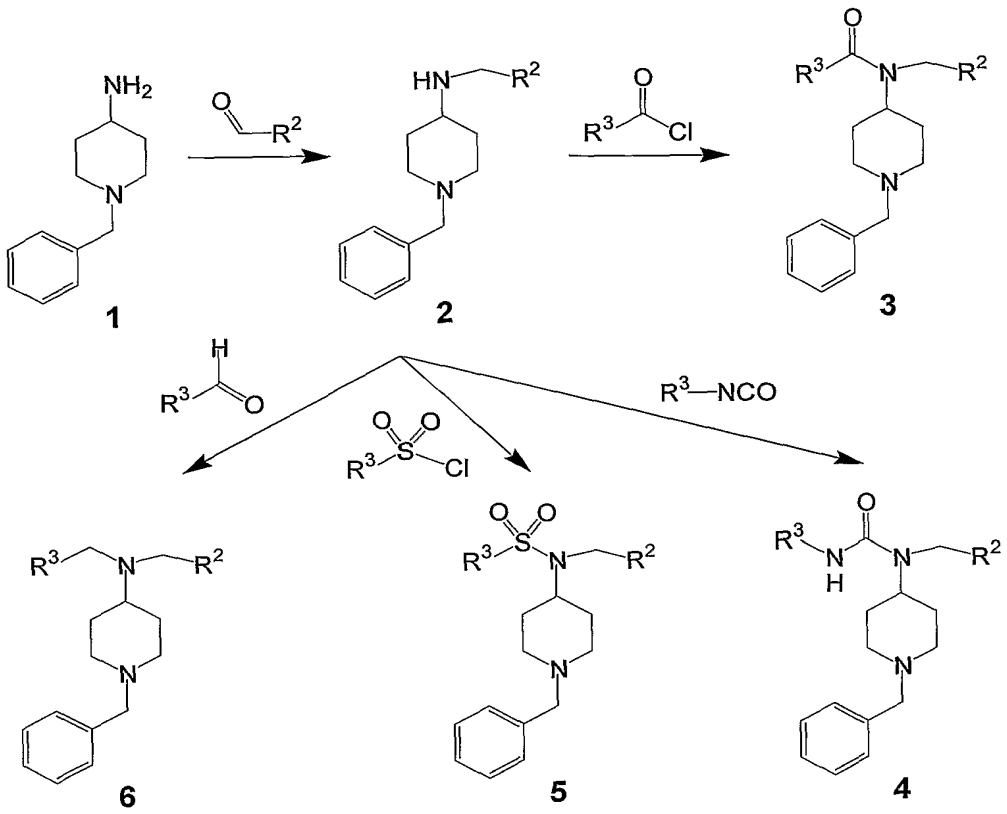
and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

A group of especially preferred novel compounds according to **formula XI** are compounds wherein R^1, R^2, R^3, **Z** and **A** are as defined in **general formula I** above and wherein **X** represents $-((C=O)-(CH_2)_q)-$ and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

Another group of especially preferred novel compounds according to **formula XI** are compounds wherein R^1, R^2, R^3, **Z** and **A** are as defined in **general formula I** above and wherein **X** represents $-((C=O)-NH-(CH_2)_q)-$ and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

The compounds of the **general formula I** of the present invention may be prepared according to the procedures and general sequences of reactions outlined below, wherein $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, **A**, **X** and **Z** are as defined in **general formula I** above (for simplicity and clarity reasons, only parts of the synthetic possibilities which lead to compounds of formulae I-XI are described). For general methods of certain steps see also pages 37-40 and WO 02/24649.

Scheme 1: Preparation of substituted 4-amino-N-benzyl-piperidines:



Typical procedure for the reductive amination (Synthesis of compounds **2**):

The amine (**1**) and the aldehyde {R^2-CHO} (1.5 eq.) are mixed in anhydrous methanol and stirred for 6 h. The mixture is then treated with sodium borohydride (1.5 eq.) and stirred for 2 h. Purified Amberlyst 15 or another suitable scavenger is added and the suspension is shaken for 12 h. The resin is then separated by filtration and washed with methanol. The secondary amine **2** is removed from the resin by adding a 2 M methanolic ammonia solution. The resin is drained after 30 min and washed with methanol. The filtrate is evaporated to yield the pure secondary amine **2**.

Typical procedure for the acylation (Synthesis of compounds **3**):

To a solution of the amine **2** in anhydrous ethyl acetate is added vacuum dried Amberlyst 21 or another suitable scavenger followed by the addition of the carboxylic acid chloride {R^3-(CO)-Cl} (1.5 eq.). After shaking the suspension for 2 h, an aliquot of water is added in order to hydrolyze the excess of the carboxylic acid chloride and shaking is continued for 1 h. The resin is then removed by filtration, washed with ethyl acetate and the solution is evaporated to yield the pure amide **3**.

The carboxylic acid chlorides {R^3-(CO)-Cl} may be obtained *in situ* from the corresponding carboxylic acid as described in the literature (i. e.: Devos, A.; Rémion, J.; Frisque-Hesbain, A.-M.; Colens,A.; Ghosez, L., *J. Chem. Soc., Chem. Commun.* **1979**, 1180).

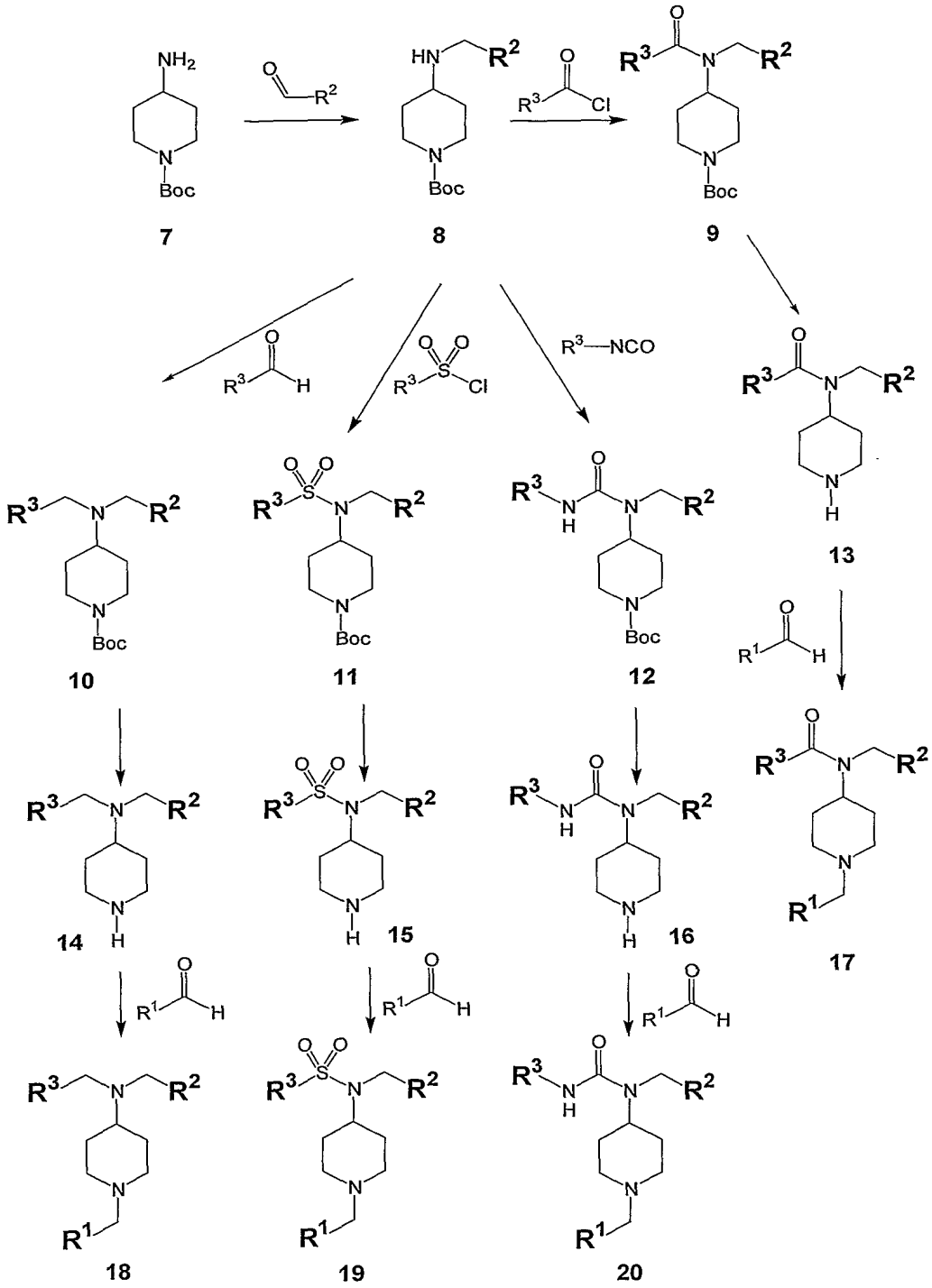
The synthesis of the sulfonamide derivatives **5** from the amine **2** is performed in analogy to the above described procedure.

The urea derivatives **4** are obtained by reaction of the amines **2** in dichloromethane, with one equivalent isocyanate.

Typical procedure for the second reductive amination (Synthesis of compound **6**):

The amine (**2**) and the aldehyde {R^3CHO} (1.5 eq.) are mixed in anhydrous dichloromethane and sodium triacetoxyborohydride (1.3 eq.) is added. After stirring the solution for 48h, methanol is added and the reaction mixture is treated in the same manner as described for amines **2**. Further experimental details on reductive aminations can be found in the literature: A. F. Abdel-Magid et al; *J. Org. Chem.*; **1996**, *61*, 3849 - 3862; K. A. Neidigh et al; *J. Chem. Soc. Perkin Trans. 1*; **1998**, 2527 - 2531; B. J. Lavey et al; *J. Org. Chem.*; **1996**, *61*, 7633 - 7636.

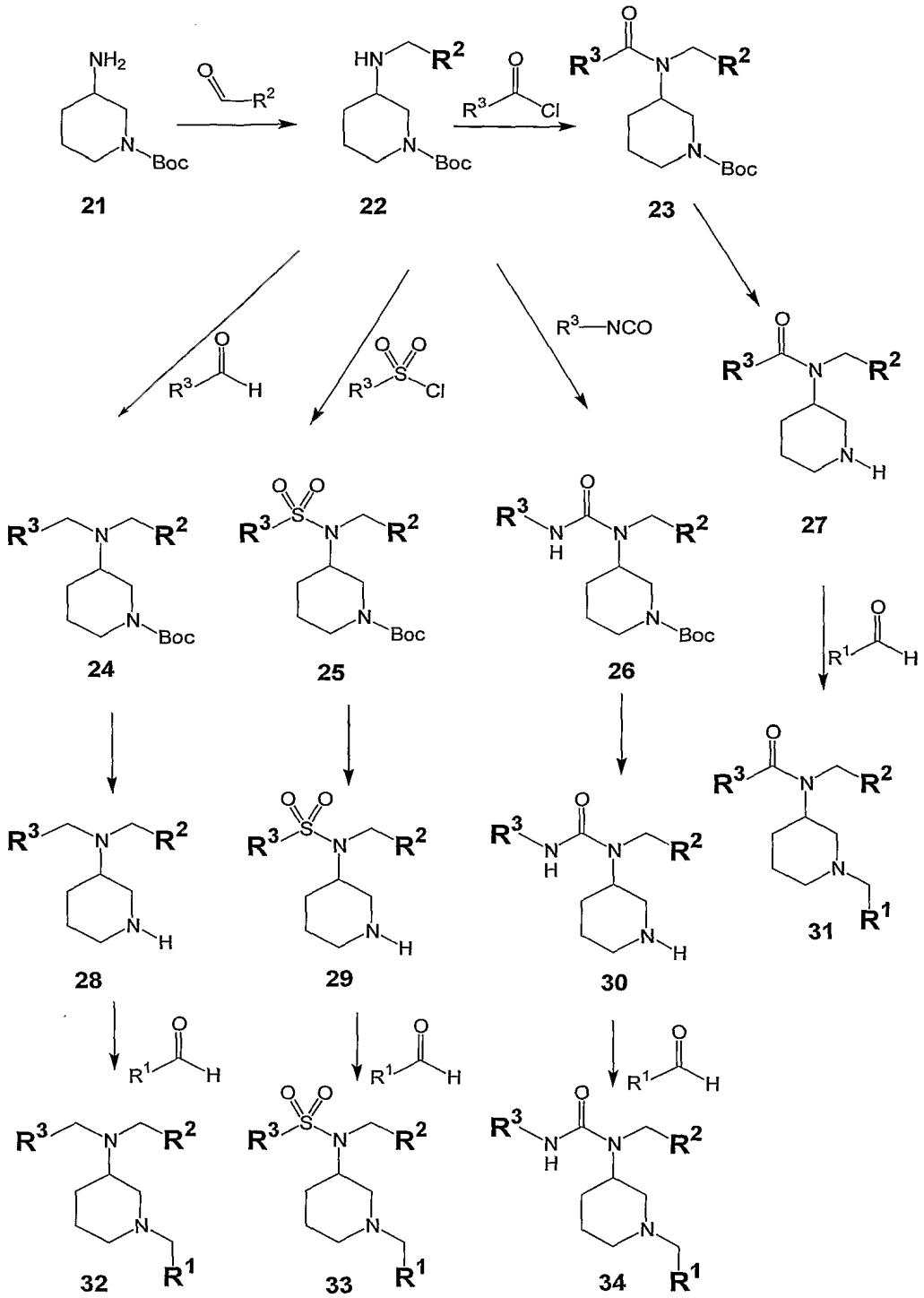
Scheme 2: Preparation of substituted 4-amino-N-(lower alkyl-aryl)-piperidines:



The N-Boc protected 4-amino-piperidine **7** (Scheme 2) can be prepared in a two step procedure starting by reacting 4-hydroxy-N-Boc-piperidine with methanesulfonylchloride in an inert solvent like DCM in the presence of a base like TEA to generate 4-mesyloxy-N-Boc-piperidine. The mesyloxy group is substituted with sodium azide followed by reduction of the azide functionality to the amino group to give **7**. The amine **7** is transformed to the secondary amine **8** via the typical procedure for the reductive amination described above. The synthesis of compounds **9**, **10**, **11** and **12** can also be performed via the typical procedures described above. Boc-deprotection is achieved either with hydrochloric acid in a solvent like diethylether or dioxane or with TFA in DCM. The second reductive amination step of the derivatives **13**, **14**, **15** and **16** to the fully derivatized final compounds **17**, **18**, **19** and **20** can be performed according to the typical procedure described above (see also: A. F. Abdel-Magid et al; *J. Org. Chem.*; **1996**, *61*, 3849 - 3862; K. A. Neidigh et al; *J. Chem. Soc. Perkin Trans. 1*; **1998**, 2527 - 2531; B. J. Lavey et al; *J. Org. Chem.*; **1996**, *61*, 7633 - 7636.).

Compounds based on the 3-amino-piperidine template (see Scheme 3) can be prepared by using 3-amino-N-Boc-piperidine as starting material, which can be prepared as described for **7**. All other chemical transformations can be performed as described above in Scheme 2.

Scheme 3: Preparation of substituted 3-amino-N-(lower alkyl-aryl)-piperidines:



Alternative Methods for the Preparation of the Fully Substituted Final Target Compounds:

Preparation of the fully substituted final target compounds (Schemes 2 and 3 give a graphical survey) started at the exocyclic amino group. The first substituent R^3 was introduced via reductive amination [Ahmed F. Abdel-Magid et al; *J. Org. Chem.*; **1996**, *61*, 3849; Clinton F. Lane; *Synthesis*; **1975**, 135] by refluxing the aldehyde and the amine in methanol for 4 h. Then the reaction mixture was cooled to rt and sodium borohydride was slowly added followed again by refluxing for 2 h. Water was added and the product was extracted either by EtOAc or DCM. The organic layers were dried and the solvents were evaporated. Purification of the product was usually achieved by column chromatography on silicagel with an appropriate mixture of EtOAc / hexane or by recrystallization from diethylether or methyl-tert.-butyl ether to give derivatives **8 / 22** in moderate to good yields. Compounds **8 / 22** were subsequently acylated by either acid chlorides, carboxylic acids (+ activation reagent like PyBOP or 1-chloro-N,N,2-trimethylpropenylamine[Acros Organics 30027-0050]) for the preparation of derivatives **9 / 23**, or sulfonyl chlorides for the preparation of derivatives **11 / 25**, in solvents like DCM, chloroform or 1,2-dichloroethane at rt or slightly elevated temperatures in the presence of a base like Hünig's base, TEA or NMO. Reactions usually run for 4 to 24 h followed by aqueous work up with saturated sodium carbonate solution. The combined organic extracts were dried and the solvents were evaporated. Purification of the compounds was achieved by column chromatography on silica gel with an appropriate solvent mixture depending on the polarity of the products or by recrystallization. Compounds **8 / 22** were also reacted with isocyanates for the preparation of derivatives **12 / 26**, in solvents like DCM, chloroform or 1,2-dichloroethane at rt or slightly elevated temperatures. Reactions usually run for 4 to 24 h. The reaction mixtures were concentrated in vacuo and the products purified by column chromatography on silica gel with an appropriate solvent mixture depending on the polarity of the products or by recrystallization. Finally the intermediates **8 / 22** were submitted for a second reductive amination step on the exocyclic amino group either by an aldehyde or a ketone to give derivatives **10 / 24**. If aldehydes were used, the reaction was performed in DCM or 1,2-dichloroethane in the presence of sodium triacetoxyborohydride at rt for 6 to 12 h followed by aqueous work up with saturated sodium carbonate solution. The combined organic layers

were dried and concentrated in vacuo. The products were purified by column chromatography on silica gel with an appropriate solvent mixture depending on the polarity of the products or by recrystallization. If ketones were used, the reaction was performed by first stirring the ketone and the amine in titanium(IV) isopropoxide at rt for 4 to 8 h followed by addition of methanol and sodium borohydride. The reaction was usually complete within 1 h and aqueous work up was performed by addition of saturated sodium carbonate solution, filtration and extraction with DCM. The combined organic layers were dried and evaporated in vacuo. The products were purified by column chromatography on silica gel with an appropriate solvent mixture depending on the polarity of the products or by recrystallization [J. G. Breitenbucher et al; *Tetrahedron Lett.*; **1998**, *39*, 8207; Ahmed F. Abdel-Magid et al; *J. Org. Chem.*; **1996**, *61*, 3849]. Boc-deprotection on the intermediates **9 / 23, 10 / 24, 12 / 26** and **11 / 25** was achieved by addition of a 4 M solution of hydrogen chloride in dioxane to a solution of the respective Boc-protected intermediate in dioxane at rt. The reaction was usually finished within 1 to 3 h. The solvent was evaporated and the amine hydrohloride intermediates were dried at HV [P. J. Kocienski, *Protecting Groups*, Thieme, **1994**; T. W. Greene, P. G. M. Wuts; *Protective Groups in Organic Synthesis*, John Wiley & sons; **1991**.]. The final compounds (e.g. **17, 18, 19, 20** or **31, 32, 33** and **34**) were prepared by reductive amination of the ring nitrogen atom with aldehydes or ketones. The reactions were performed as described before for the preparation of **10 / 24**.

The following examples illustrate the invention but do not limit the scope thereof. All temperatures are stated in °C.

List of abbreviations:

Boc_2O	di-tert.-butyl-di-carbonat
Boc or boc	tert.-butyloxycarbonyl
BOP	Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium-hexafluorophosphate
BSA	bovine serum albumine
Cbz	benzyloxycarbonyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene(1,5-5)
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
HATU	O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium-hexafluorophosphate
HBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium-hexafluorophosphate
HCl	hydrogen chloride
HV	high vacuum
LAH	lithium aluminium hydride
M	molar
NMM	N-methylmorpholine
PG	protecting group
$POCl_3$	phosphorous oxychloride
PyBOP	Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
Rt or rt	room temperature

TBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetraethyluronium-tetrafluoroborate
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
tR or t_R	retention time

General Procedures and Examples:

The following compounds were prepared according to the procedures described for the synthesis of compounds encompassed by the general formulae hereinbefore. All compounds were characterized by ^{1}H-NMR (300MHz) and occasionally by ^{13}C-NMR (75MHz) (Varian Oxford, 300MHz; chemical shifts are given in ppm relative to the solvent used; multiplicities: s = singlet, d = doublet, t = triplet; m = multiplet), by LC-MS: **A**: 2 min < t_R < 10 min; (Waters Micromass; ZMD-platform with ESI-probe with Alliance 2790 HT; Colum: 2x30mm, Gromsil ODS4, 3µm, 120A; Gradient: 0 – 100% acetonitril in water, 6 min, with 0.05% formic acid, flow: 0.45ml/min; t_R is given in min.), **B**: 0.1 min < t_R < 1.5 min; (Finnigan AQA with ESI-probe with HP 110 DAD and HP110 binary pump; column: Develosil RP-AQUEOUS, 5µm, 4.6 mm x 50 mm; gradient: 5 - 95% acetonitril in water (0.04% TFA), 1 min., 95% acetonitril in water (0.04% TFA) 0.4 min., 4.5 ml/min.), by TLC (TLC-plates from Merck, Silica gel 60 F_{254}) and occasionally by melting point.

a) General Procedures:

Typical procedure A) for the reductive amination:

The amine and the aldehyde (1.5 eq.) (which are used as starting materials, are known compounds or the synthesis is described in the *Reference Examples*), are mixed in anhydrous methanol and refluxed for 4 h. The mixture is cooled to rt and then treated with sodium borohydride (1.5 eq.) and again stirred for 2 h at reflux temperature. The reaction mixture is concentrated in vacuo and water is slowly added followed by extraction with DCM (3x). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude compound is purified by column chromatography on silica gel by an appropriate mixture of EtOAc / hexane containing 1% TEA or by recrystallization from a suitable solvent.

Typical procedure B) for the acylation (with acid chlorides or sulfonylchlorides):

To a solution of the secondary amine in anhydrous DCM is added Hünig's base (10 eq) or another suitable base followed by the addition of the carboxylic acid chloride or the sulfonylchloride (1.5 eq.). The reaction mixture is stirred for 4 to 12 h at rt. Then saturated sodium carbonate solution was added and the mixture was exctracted with DCM (3x). The combined organic layers were washed with 1 N HCl and brine, dried over magnesium sulfate, filtered and evaporated. The crude compound is purified by column chromatography on silica gel by an appropriate mixture of EtOAc / hexane or by recrystallization from a suitable solvent to give the pure amide intermediates.

Typical Procedure C) for the reaction with isocyanates:

To a solution of the secondary amine in DCM was added the isocyanate (1.5 eq) and the reaction mixture was stirred at rt for 4 to 12 h. The reaction mixture was directly concentrated in vacuo and the crude material was purified by column chromatography on silica gel by an appropriate mixture of EtOAc / hexane or by recrystallization from a suitable solvent to give the pure urea intermediates.

Typical Procedure D) for the second reductive amination with aldehydes:

To a solution of the secondary amine in DCM was added the aldehyde (1.5 eq) and sodium triacetoxy borohydride (4 eq). Stirring was continued for 6 to 12 h. Water was added and the mixture was extracted with DCM (3x). The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo and the crude material was purified by column chromatography on silica gel by an appropriate mixture of EtOAc / hexane or by recrystallization from a suitable solvent to give the pure tertiary amine intermediates.

Typical Procedure E) for the second reductive amination with ketones:

To a solution of the secondary amine in neat titanium tetra-isopropoxide was added the ketone (1.5 eq). The mixture was stirred for 4 h at rt followed by addition of methanol and sodium borohydride (4 eq). Stirring was continued for 1 hour. Water was added and the mixture was extracted with DCM (3x). The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo and the crude material was purified by column chromatography on silica gel by an appropriate mixture of EtOAc / hexane or by recrystallization from a suitable solvent to give the pure tertiary amine intermediates.

Typical procedure F) for the Boc-deprotection:

To a solution of the Boc-protected amine in dioxane at rt was added a solution of 4 M HCl in dioxane (commercially available from Aldrich). Stirring was continued for 1 to 5 h. The mixture was evaporated and dried at HV to give the pure HCl salt of the secondary amine which were used without further purification.

Typical procedure G) for the reductive amination of the ring-nitrogen atom of the piperidine system:

- If aldehydes were used, the method described as *Typical Procedure D)* was applied:
- If ketones were used, the method described as *Typical Prodedure E)* was applied.
- If ketones were used, the reaction could also be performed as follows:

To a solution of the secondary amine in methanol was added the ketone (1.5 eq) and sodium cyano borohydride (6 eq) and some drops of acetic acid or hydrochloric acid. Stirring was continued for 6 to 12 h. Water was added and the mixture was extracted with DCM (3x) or EtOAc (3x). The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo and the crude material was purified by column chromatography on silica gel by an appropriate mixture of EtOAc / hexane or by recrystallization from a suitable solvent to give the pure tertiary amines as final compounds.

Typical procedure H) for the Suzuki coupling with arylbromides:

To a solution of arylbromide in toluene is added the boronic acid (1.1 eq.) in isopropanol and a 2M aqueous solution of potassium carbonate (5 eq.). The mixture is purged with nitrogen for 10 min and tetrakis(triphenylphosphine) palladium (0.03 eq.) is added. After heating under reflux for 6 h, water is added to the cooled reaction mixture and the product is extracted with ethyl acetate. The organic phase is washed with brine and dried over sodium sulfate. The solvent is evaporated to give the crude aldehyde, which is purified by flash chromatography (EtOAc/heptane gradient).

Typical procedure I) for the Suzuki coupling with arylchlorides:

The arylchloride, the boronic acid (1.5 eq) and potassium phosphate (K3PO4; 3 eq)) were added subsequently to dioxane (5 ml / mmol arylchloride). While heating to 100°C, nitrogen is bubbled through the mixture. Then a solution of 2'-(dimethylamino)-2-biphenylyl-palladium(II)-chloride dinorbornylphosphine-complex (from Solvias or Fluka 36037; 0.01 eq)) was added to the hot reaction mixture and stirring was continued for 6 to 18 h. The reaction mixture is cooled to rt, water is added and the product extracted with EtOAc. The combined organic layers were dried with magnesium sulfate, filtered and concentrated in vacuo. The crude product is purified by flash chromatography (EtOAc/heptane gradient).

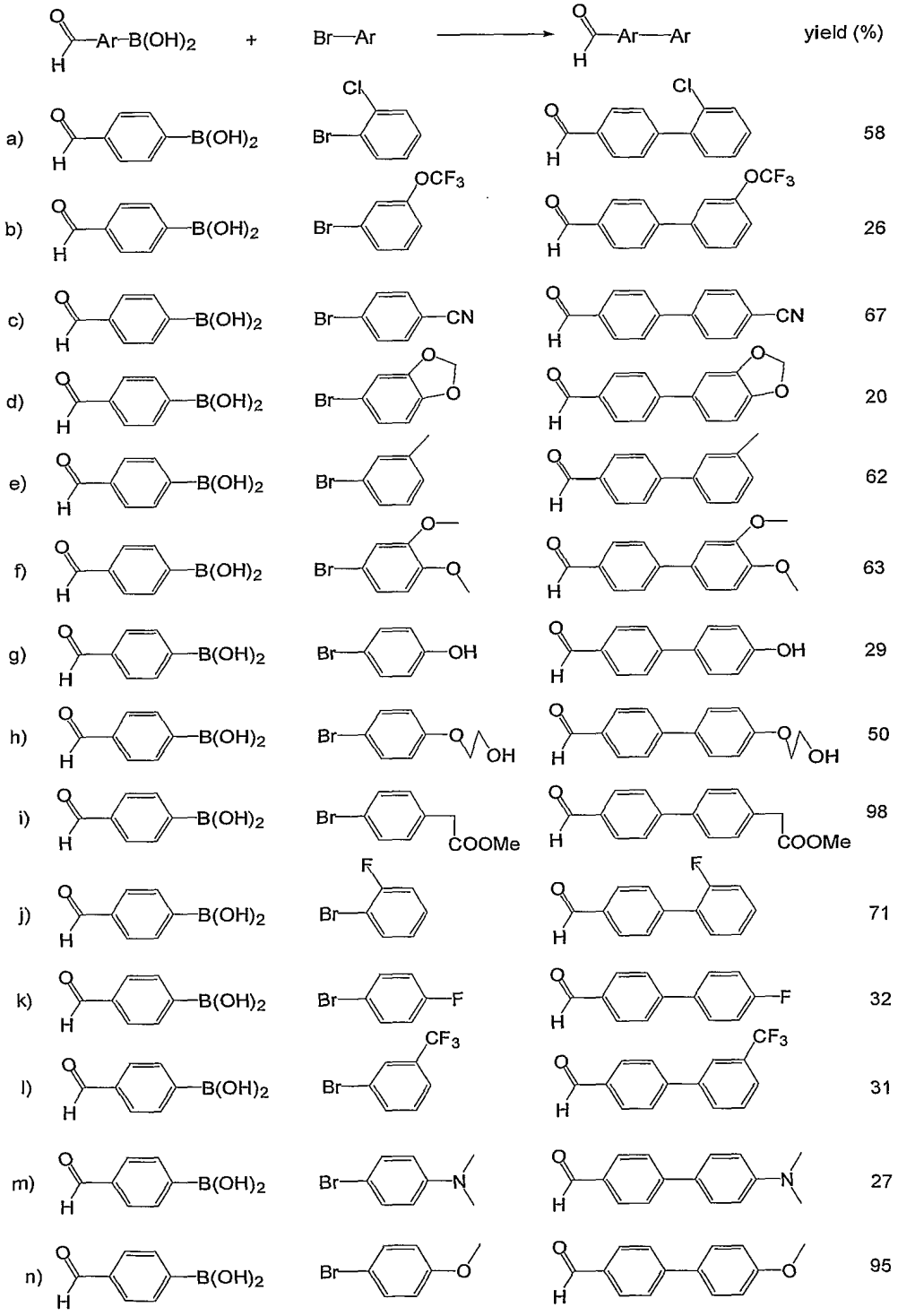
Typical Procedure K) for the Sonogashira coupling of terminal acetylenes with aryliodides:
Stephan Thorand, Norbert Krause, *J. Org. Chem.*, **1998**, *63*, 8551-8553.
D. Trachsel, *Helv. Chim. Acta.*, **2003**, in press.

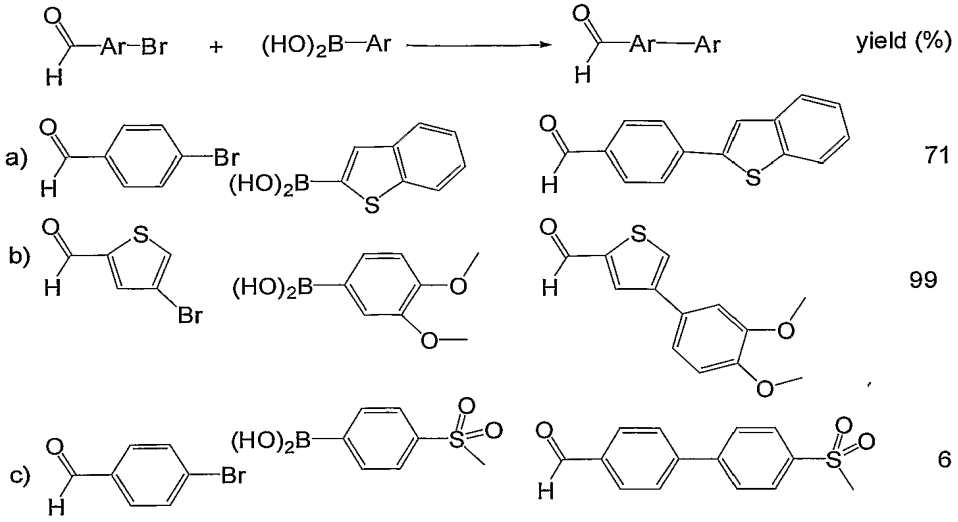
Typical Procedure L) for the Sonogashira coupling of terminal acetylenes with arylbromides:
G. Reginato, A. Mordini, M. Caracciolo; *J. Org. Chem.*; **1997**, *62*, 6187-6192.

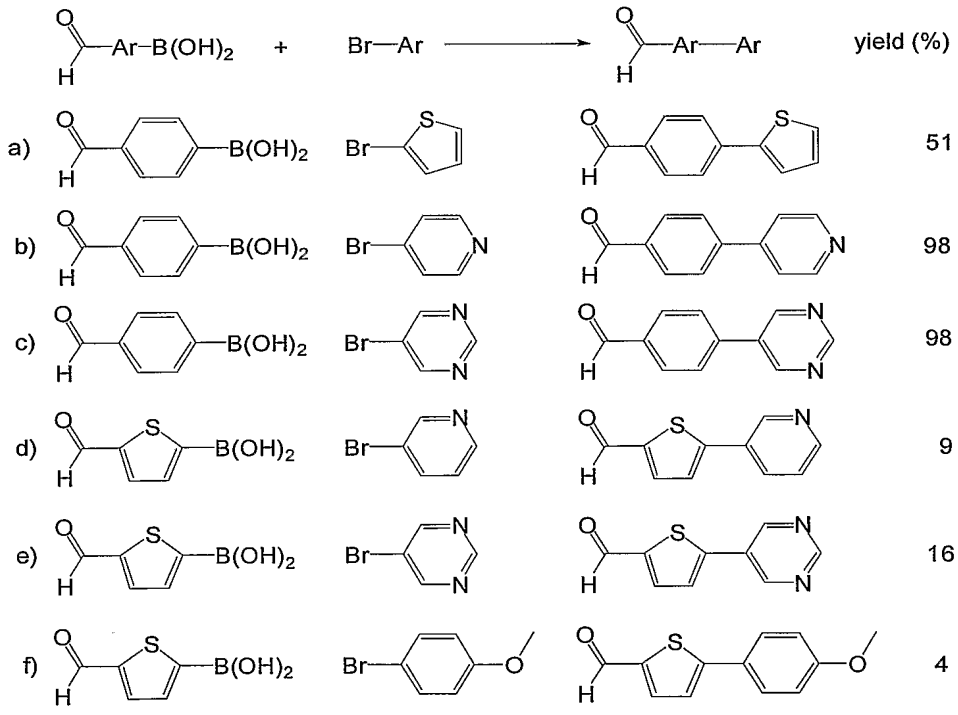
Typical Procedure M) for the preparation of alkyl substituted aryl- and heteroaryl units:
A. Fürstner, A. Leitner, M. Mendez, H. Krause; *J. Am. Chem. Soc.*; **2002**, *124*, 13856-13863.

Typical Procedure N) for the acylation with carboxylic acids:
To a solution of the carboxylic acid (1.5 eq) in DCM or acetonitrile was added a coupling reagent auch as TBTU, HBTU, HATU, PyBOP, BOP and the like (1.5 eq), the respective secondary amine (1 eq) and Hünig`s base (10 eq). Stirring was continued at rt. for 8h to 16 h. Work up was performed as described in *Typical Procedure B)*.

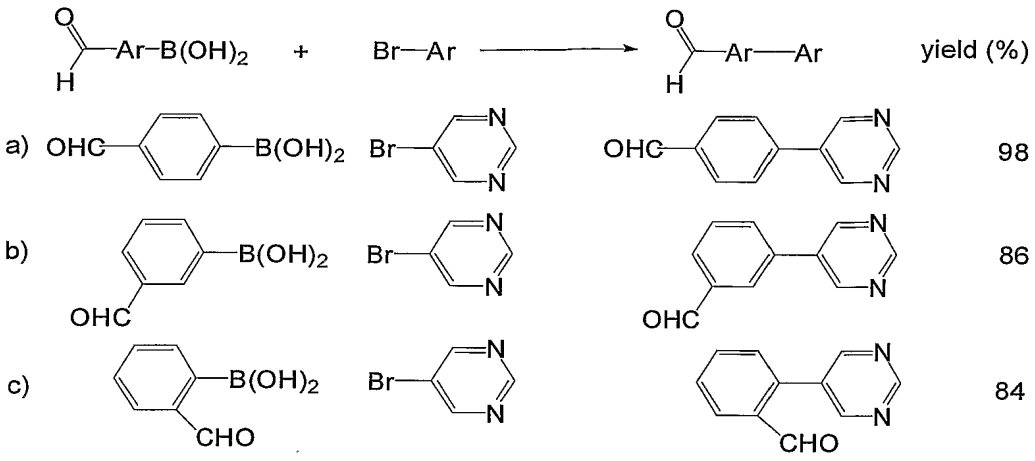
Referential Example 1: ***Biaryl-aldehydes:***



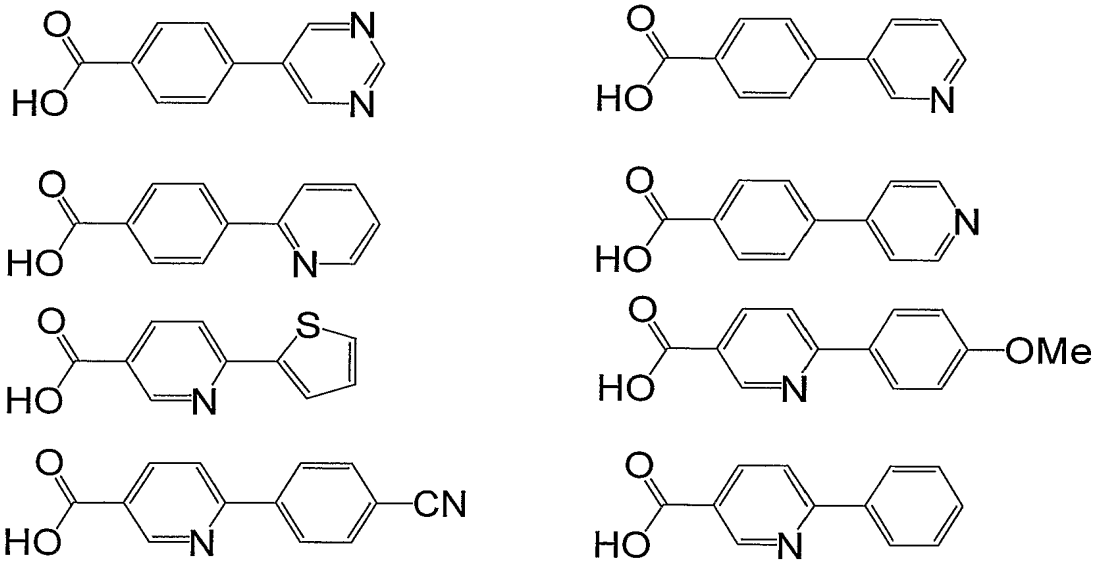

Ar–Br + (HO)2B–Ar
Ar–Ar
yield (%)
a)
71
b)
99
c)
6


Ar–B(OH)2 + Br–Ar
Ar–Ar
yield (%)
a)
51
b)
98
c)
98
d)
9
e)
16
f)
4

5



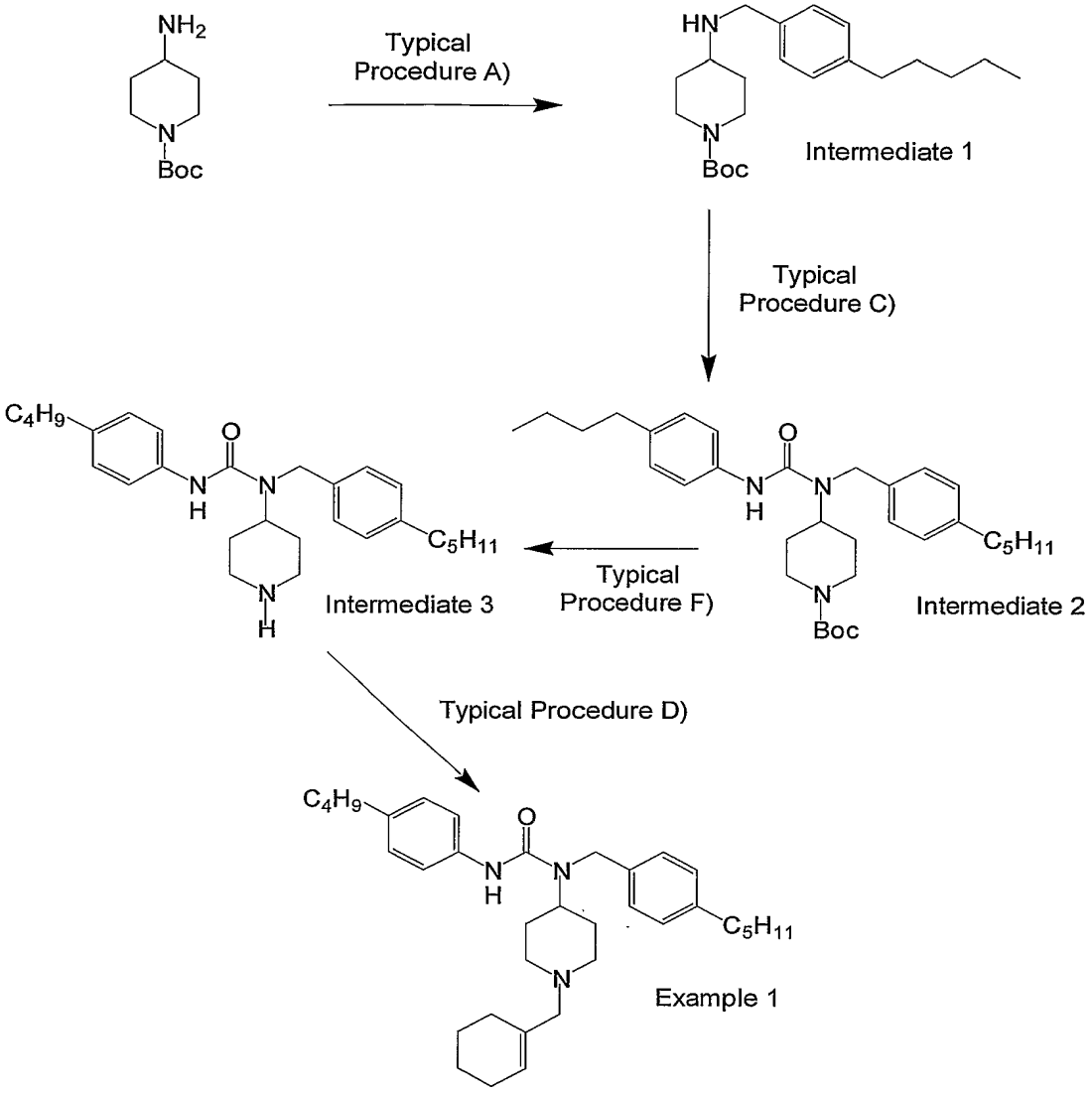
Biaryl-carboxylic acids:



The commercially not available biaryl-, heteroaryl-aryl-, aryl-heteroaryl- and heterobiaryl-substituents can be prepared according to *Typical Procedures H)* and *I)* or according to methods described in [WO 02/24649 or A. F. Littke and G. C. Fu; *Angew. Chem.*; **1998**, *110*, 3586 and references cited there]. Referential Example 1 only gives an illustrative overview of such substituents and does not limit the invention towards the structures depicted above. For the preparation of the biaryl-carboxylic acids see also [Y. Gong and H. W. Pauls; *Synlett*, **2000**, 829.]

c) Examples:

Example 1:

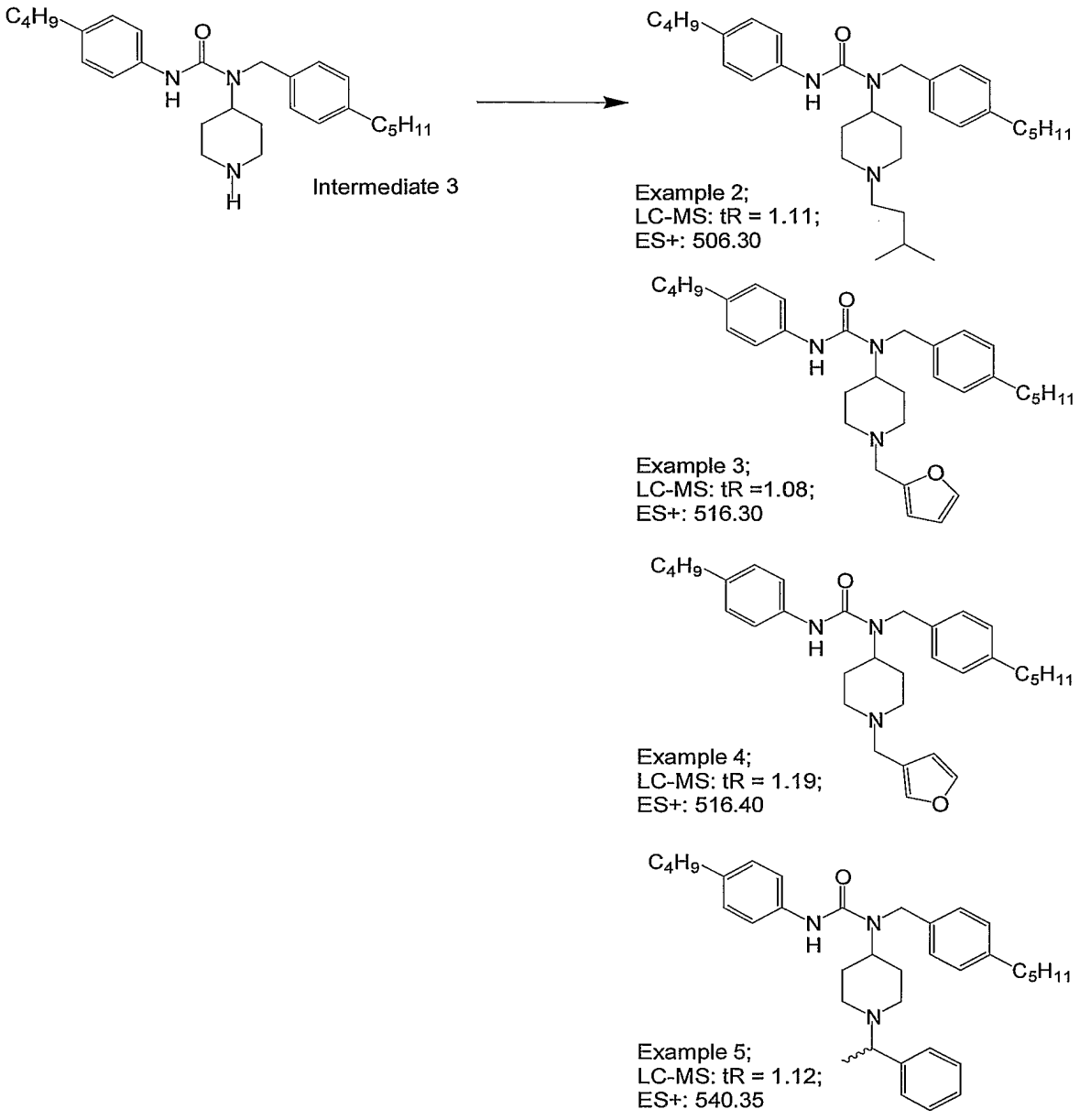


3-(4-Butyl-phenyl)-1-(1-cyclohex-1-enylmethyl-piperidin-4-yl)-1-(4-pentyl-benzyl)-urea

Intermediate 1 was prepared from N-Boc-4-aminopiperidine and 4-pentylbenzaldehyde according to Typical Procedure A) and transformed to Intermediate 2 by reaction with 2-butylphenylisocyanate according to Typical Procedure C). Dprotection was achieved by 4 M

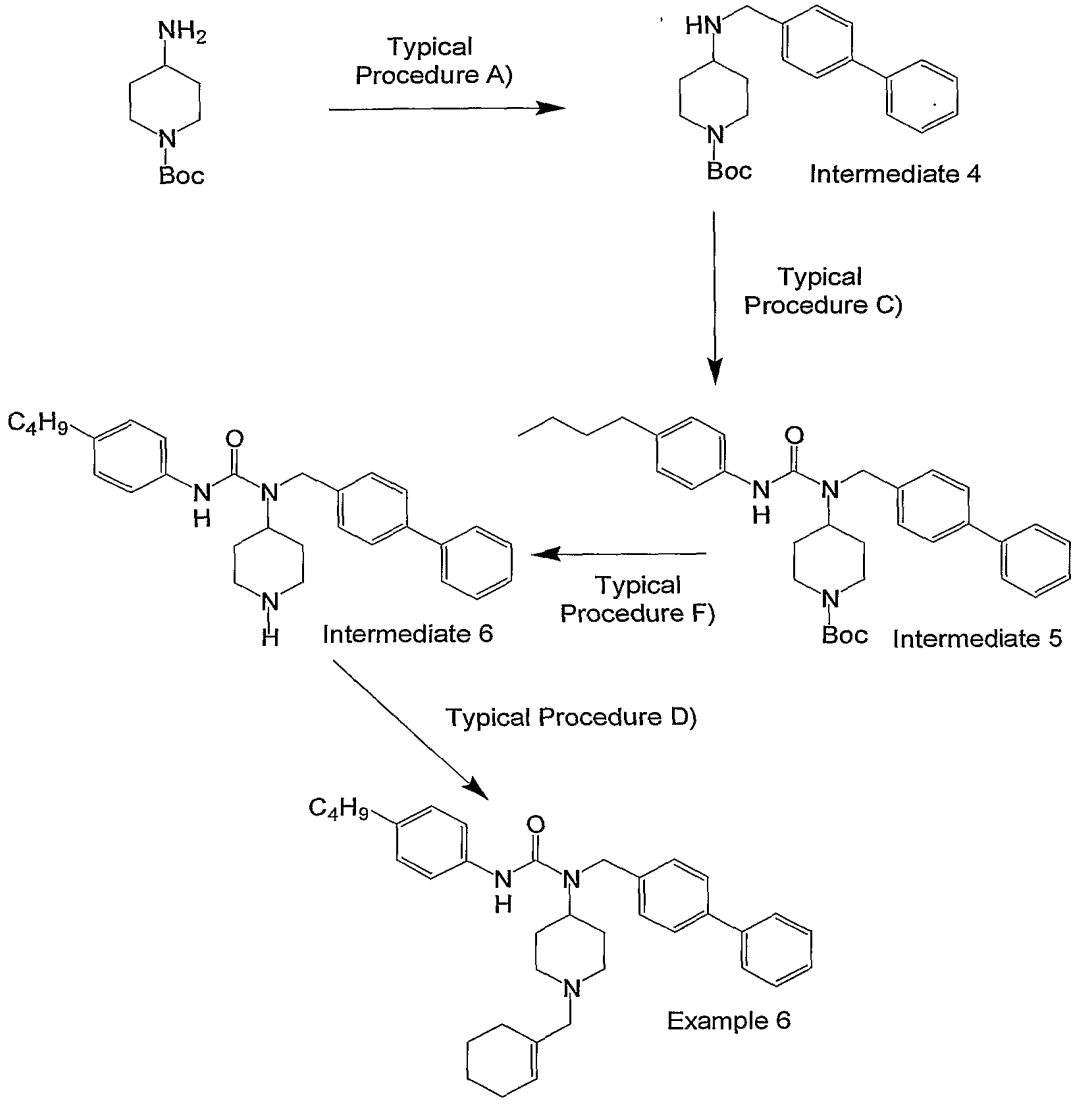
HCl in dioxane (Typical Procedure F)) to give Intermediate 3 which was subsequently transformed to Example 1 by reaction with cyclohexene-1-carboxaldehyde according to Typical Procedure D). LC: t_R = 1.13 min; MS: ES+ = 530.34.

Chart 1:



Example 2, Example 3, Example 4 and Example 5 were prepared from Intermediate 3 by reaction with iso-valeraldehyde, furane-2-carboxaldehyde, furane-3-carboxaldehyde and acetophenone, respectively according to Typical Procedure D) (Example 2, Example 3, Example 4) and according to Typical Procedure E) (Example 5).

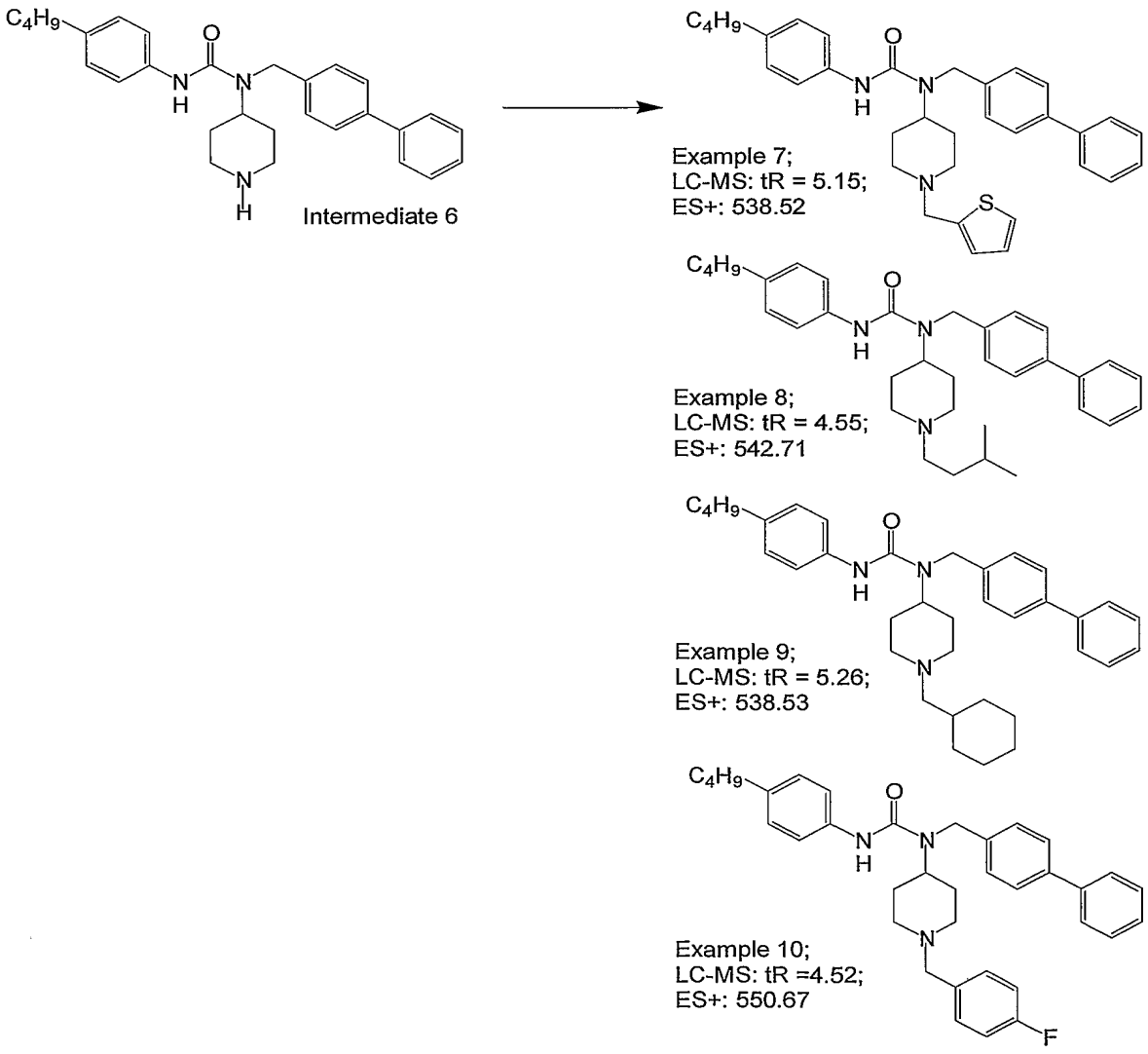
Example 6:



1-Biphenyl-4-ylmethyl-3-(4-butyl-phenyl)-1-(1-cyclohex-1-enylmethyl-piperidin-4-yl)-urea

Intermediate 4 was prepared from N-Boc-4-aminopiperidine and 4-biphenylcarboxaldehyde according to Typical Procedure A) and transformed to Intermediate 5 by reaction with 2-butylphenylisocyanate according to Typical Procedure C). Dprotection was achieved by 4 M HCl in dioxane (Typical Procedure F)) to give Intermediate 6 which was subsequently transformed to Example 6 by reaction with cyclohexene-1-carboxaldehyde according to Typical Procedure D). LC: t_R = 4.65 min; MS: ES+ = 536.46.

Chart 2:



Example 7, Example 8, Example 9 and Example 10 were prepared from Intermediate 6 by reaction with thiophene-2-carboxaldehyde, iso-valeraldehyde cyclohexane-carboxaldehyde and 4-fluoro-benzaldehyde, respectively according to Typical Procedure D).

5

According to the Typical Procedures A) to N) given above, the descriptions given above and the descriptions given in the cited literature the Examples 11 to 139 depicted in charts 3 to 20 were prepared.

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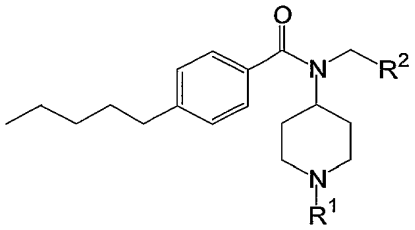
Chart 3:



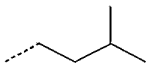
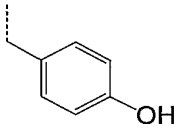
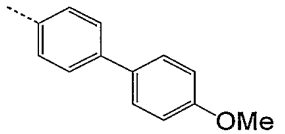
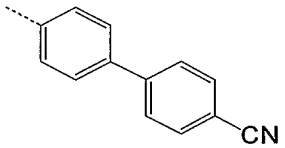
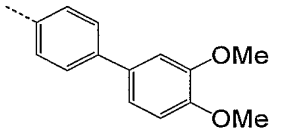
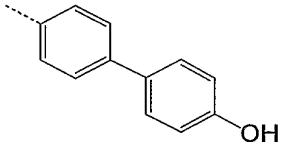
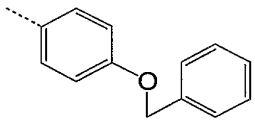
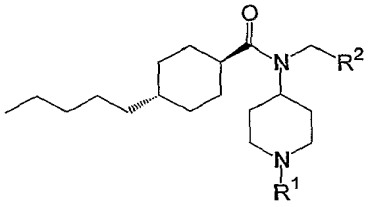
R^2 \ R^1		
	Example 11; LC-MS: tR =4.32; ES+: 541.74	Example 16; LC-MS: tR = 4.40; ES+: 577.77
	Example 12; LC-MS: tR = 4.19; ES+: 536.88	Example 17; LC-MS: tR =4.14; ES+: 572.84
	Example 13; LC-MS: tR =4.19; ES+: 571.89	Example 18; LC-MS: tR = 4.35; ES+: 607.83
	Example 14; LC-MS: tR = 0.97; ES+: 527.44	Example 19; LC-MS: tR = 4.30; ES+: 563.68
	Example 15; LC-MS: tR = 4.43; ES+: 541.85	Example 20; LC-MS: tR = 4.41; ES+: 577.84

Chart 4:



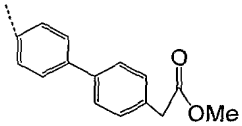
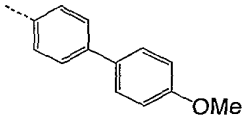
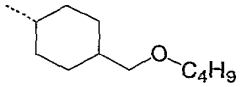
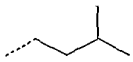
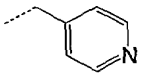
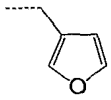
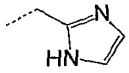
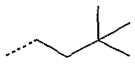
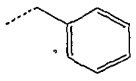
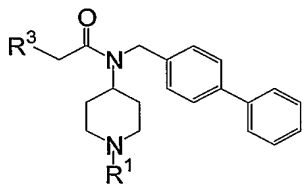
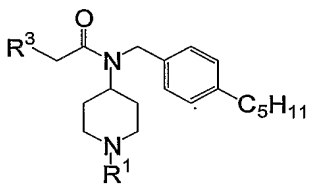
R^1 \ R^2			
	Example 21; LC-MS: tR = 1.11; ES+: 589.54		
	Example 22; LC-MS: tR = 0.96; ES+: 610.51	Example 26; LC-MS: tR = 4.63; ES+: 568.91	
	Example 23; LC-MS: tR = 1.07; ES+: 599.49		
	Example 24; LC-MS: tR = 0.99; ES+: 599.51		
		Example 25; LC-MS: tR = 6.27; ES+: 561.80	
			Example 27; LC-MS: tR = 1.24; ES+: 553.40

Chart 5:





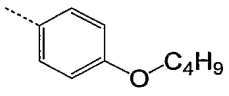
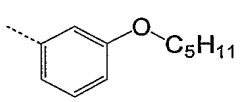
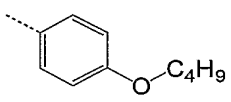
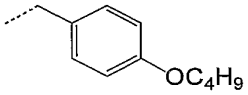
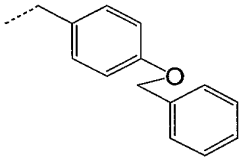
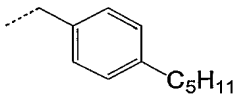
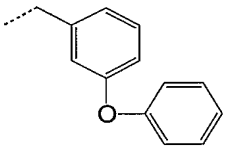
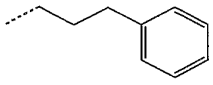
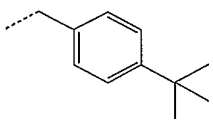
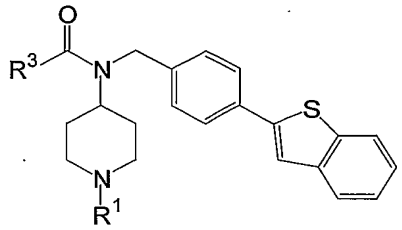
R^1 \ R^3			
	Example 28; LC-MS: tR = 1.14; ES+: 619.22	Example 34; LC-MS: tR = 1.18; ES+: 633.17	Example 40; LC-MS: tR = 1.21; ES+: 613.23
	Example 29: LC-MS: tR = 1.13; ES+: 653.17	Example 35; LC-MS: tR = 1.17; ES+: 667.16	Example 41; LC-MS: tR = 1.20; ES+: 647.22
	Example 30; LC-MS: tR = 1.17; ES+: 617.24	Example 36; LC-MS: tR = 1.21; ES+: 631.20	Example 42; LC-MS: tR = 1.24; ES+: 611.25
	Example 31; LC-MS: tR = 1.12; ES+: 639.17	Example 37; LC-MS: tR = 1.17; ES+: 653.11	Example 43; LC-MS: tR = 1.19; ES+: 633.22
	Example 32; LC-MS: tR = 1.09; ES+: 575.19	Example 38; LC-MS: tR = 1.13; ES+: 589.18	Example 44; LC-MS: tR = 1.16; ES+: 569.22
	Example 33; LC-MS: tR = 1.13; ES+: 603.22	Example 39; LC-MS: tR = 1.18; ES+: 617.19	Example 45; LC-MS: tR = 1.21; ES+: 597.25

Chart 6:



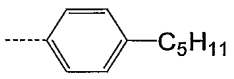
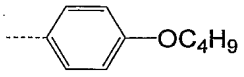
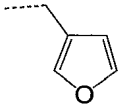
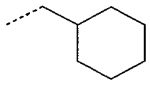
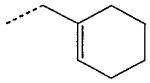
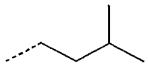
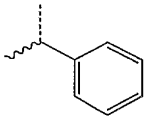
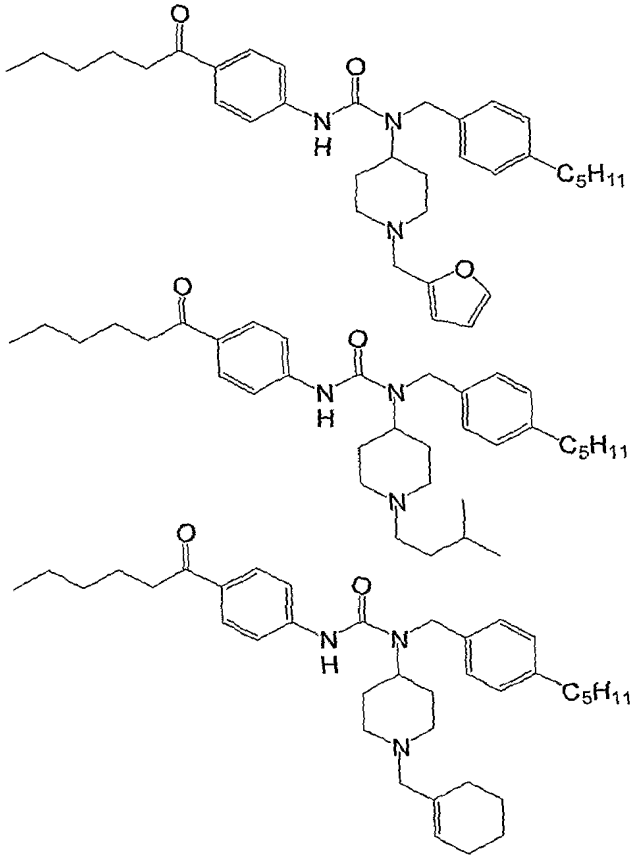
R^1 \ R^3		
	Example 46; LC-MS: tR = 4.99; ES+: 577.29	Example 49; LC-MS: tR =4.80; ES+: 579.26
		Example 50; LC-MS: tR = 5.05; ES+: 595.81
		Example 51; LC-MS: tR = 5.08; ES+: 593.32
	Example 47; LC-MS: tR = 5.35; ES+: 567.36	Example 52; LC-MS: tR = 5.20; ES+: 569.29
	Example 48; LC-MS: tR = 5.44; ES+: 601.43	Example 53; LC-MS: tR = 5.49; ES+: 603.89

Chart 7:

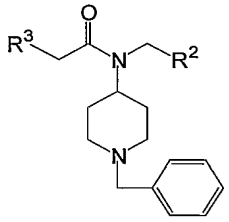


Example 54;
LC-MS: tR = 5.34;
ES+: 560.85

Example 55;
LC-MS: tR = 5.48;
ES+: 550.74

Example 56;
LC-MS: tR = 5.85;
ES+: 574.79

Chart 8:



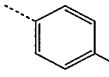
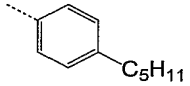
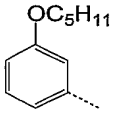
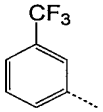
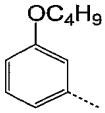
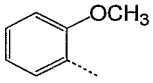
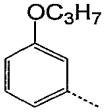
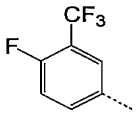
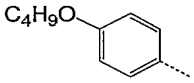
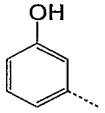
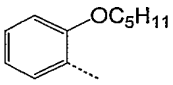
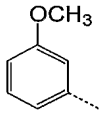
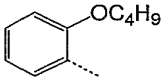
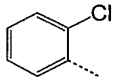
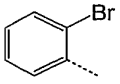
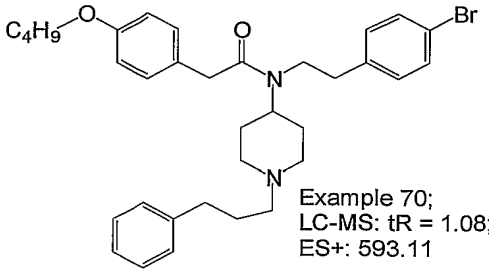
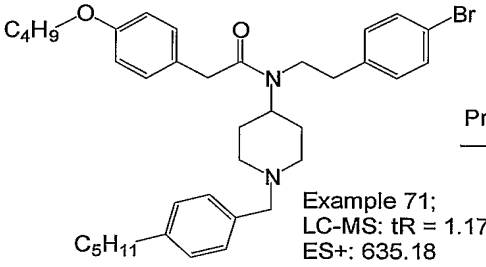
R^3 \ R^2 = 		R^3 \ R^2 = 	
	Example 57; LC-MS: tR = 1.18; ES+: 555.26		Example 64; LC-MS: tR = 1.10; ES+: 537.15
	Example 58; LC-MS: tR = 1.15; ES+: 541.25		Example 65; LC-MS: tR = 1.06; ES+: 500.28
	Example 59; LC-MS: tR = 1.11; ES+: 527.22		Example 66; LC-MS: tR = 1.11; ES+: 555.13
	Example 60; LC-MS: tR = 5.10; ES+: 541.49		Example 67; LC-MS: tR = 0.98; ES+: 485.18
	Example 61; LC-MS: tR = 1.19; ES+: 555.23		Example 68; LC-MS: tR = 4.68; ES+: 499.33
	Example 62; LC-MS: tR = 1.17; ES+: 541.21		Example 69; LC-MS: tR = 4.73; ES+: 503.28
	Example 63; LC-MS: tR = 4.67; ES+: 549.29		

Chart 9:

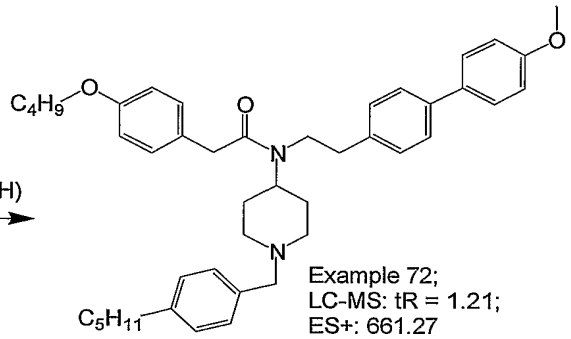


Example 70;
LC-MS: tR = 1.08;
ES+: 593.11

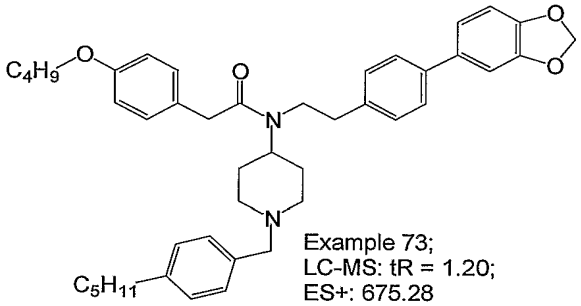


Example 71;
LC-MS: tR = 1.17;
ES+: 635.18

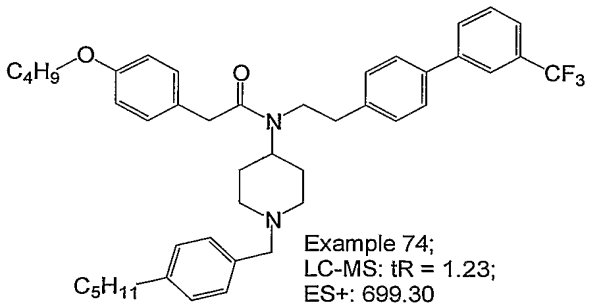
Typical Procedure H)



Example 72;
LC-MS: tR = 1.21;
ES+: 661.27

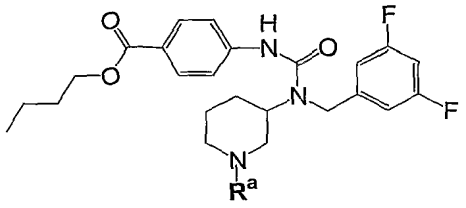


Example 73;
LC-MS: tR = 1.20;
ES+: 675.28



Example 74;
LC-MS: tR = 1.23;
ES+: 699.30

Chart 10:



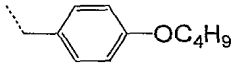
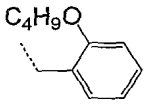
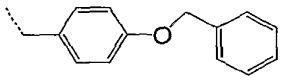
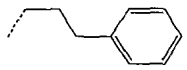
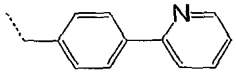
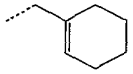
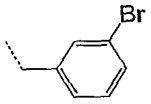
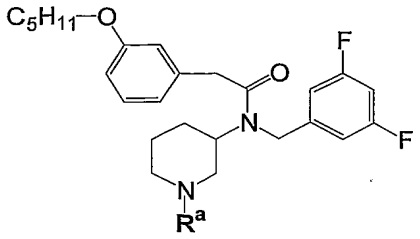
R^a	Data
	Example 75 LC-MS: tR = 0.97 ES+ = 608.27
	Example 76 LC-MS: tR = 0.99 ES+ = 608.28
	Example 77 LC-MS: tR = 0.97 ES+ = 642.34
	Example 78 LC-MS: tR = 0.94 ES+ = 564.26
	Example 79 LC-MS: tR = 0.86 ES+ = 613.30
	Example 80 LC-MS: tR = 0.93 ES+ = 540.26
	Example 81 LC-MS: tR = 0.94 ES+ = 614.20

Chart 11:



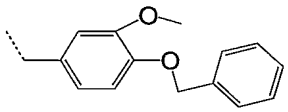
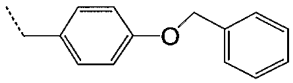
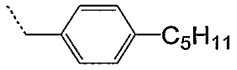
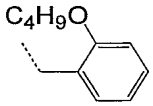
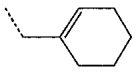
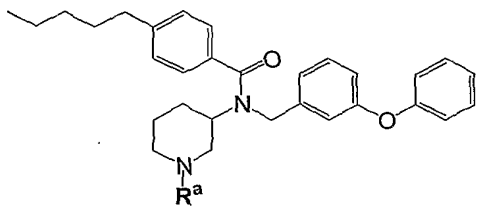
R^a	Data
	Example 82 LC-MS: tR = 1.00 ES+ = 657.30
	Example 83 LC-MS: tR = 1.00 ES+ = 627.31
	Example 84 LC-MS: tR = 1.03 ES+ = 591.45
	Example 85 LC-MS: tR = 1.01 ES+ = 593.44
	Example 86 LC-MS: tR = 0.96 ES+ = 525.31

Chart 12:



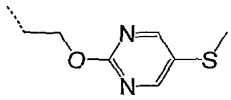
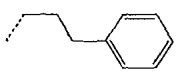
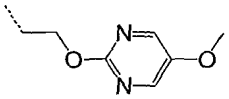
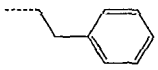
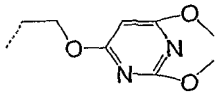
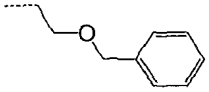
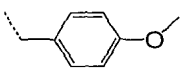
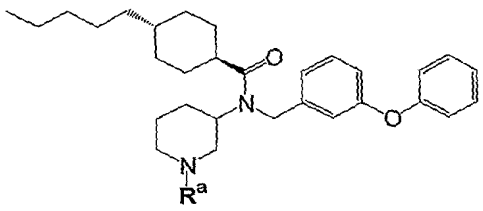
R^a	Data
	Example 87 LC-MS: tR = 1.01 ES+ = 590.41
	Example 88 LC-MS: tR = 1.00 ES+ = 625.17
	Example 89 LC-MS: tR = 1.03 ES+ = 575.39
	Example 90 LC-MS: tR = 0.98 ES+ = 609.15
	Example 91 LC-MS: tR = 1.02 ES+ = 561.41
	Example 92 LC-MS: tR = 1.01 ES+ = 639.22
	Example 93 LC-MS: tR = 1.02 ES+ = 591.27
	Example 94 LC-MS: tR = 1.00 ES+ = 577.37

Chart 13:



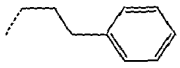
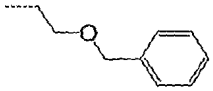
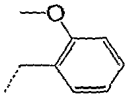
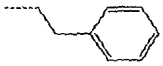
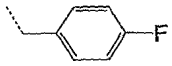
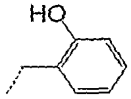
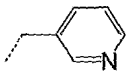
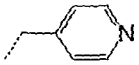
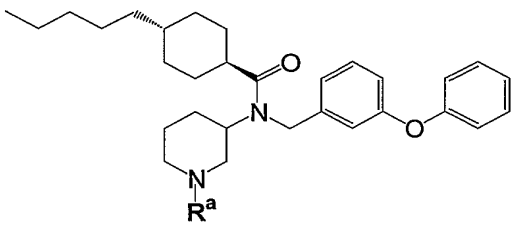
R^a	Data
	Example 95 LC-MS: tR = 1.07 ES+ = 581.40
	Example 96 LC-MS: tR = 1.06 ES+ = 597.44
	Example 97 LC-MS: tR = 1.06 ES+ = 583.40
	Example 98 LC-MS: tR = 1.06 ES+ = 567.43
	Example 99 LC-MS: tR = 1.04 ES+ = 571.41
	Example 100 LC-MS: tR = 1.02 ES+ = 569.39
	Example 101 LC-MS: tR = 0.96 ES+ = 554.43
	Example 102 LC-MS: tR = 0.99 ES+ = 554.45

Chart 14:



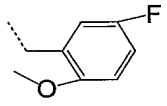
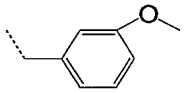
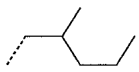
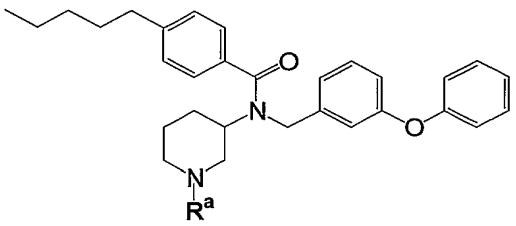
R^a	Data
	Example 103 LC-MS: tR = 1.06 ES+ = 601.43
	Example 104 LC-MS: tR = 1.05 ES+ = 583.41
	Example 105 LC-MS: tR = 1.07 ES+ = 547.48

Chart 15:



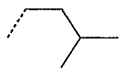
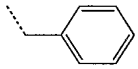
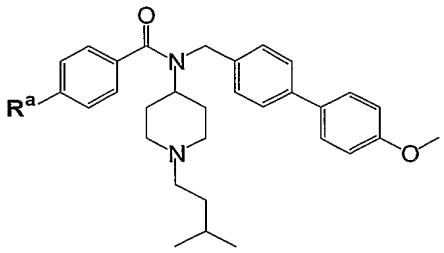
R^a	Data
	Example 106 LC-MS: tR = 1.07 ES+ = 576.4
	Example 107 LC-MS: tR = 1.08 ES+ = 513.45
	Example 108 LC-MS: tR = 1.06 ES+ = 533.43

Chart 16:



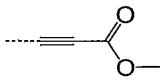
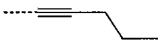
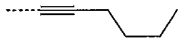
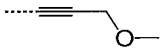
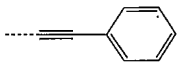
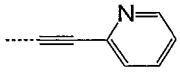
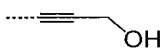
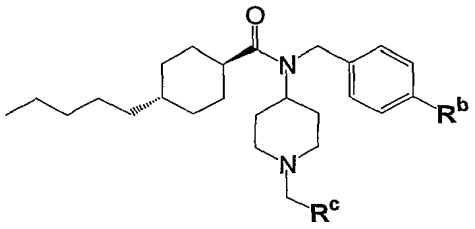
R^a	Data
	Example 109 LC-MS: tR = 0.94 ES+ = 553.32
	Example 110 LC-MS: tR = 0.99 ES+ = 537.30
	Example 111 LC-MS: tR = 1.00 ES+ = 551.28
	Example 112 LC-MS: tR = 0.99 ES+ = 551.37
	Example 113 LC-MS: tR = 0.93 ES+ = 539.25
	Example 114 LC-MS: tR = 1.00 ES+ = 571.27
	Example 115 LC-MS: tR = 0.92 ES+ = 572.27
	Example 116 LC-MS: tR = 0.87 ES+ = 525.27

Chart 17:



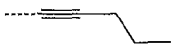
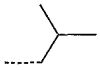
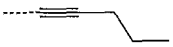
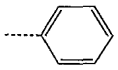
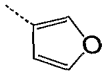
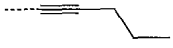
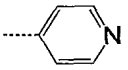
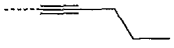
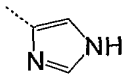
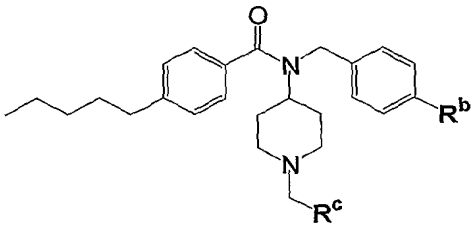
R^b	R^c	Data
		Example 117 LC-MS: tR = 1.05 ES+ = 507.59
		Example 118 LC-MS: tR = 1.05 ES+ = 527.54
		Example 119 LC-MS: tR = 1.03 ES+ = 517.51
		Example 120 LC-MS: tR = 0.96 ES+ = 528.53
		Example 121 LC-MS: tR = 0.97 ES+ = 517.52

Chart 18:



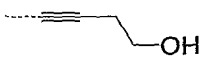
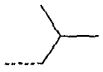
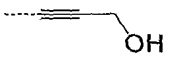
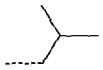
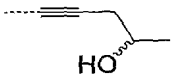
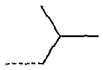
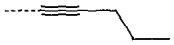
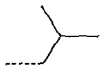
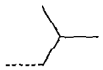
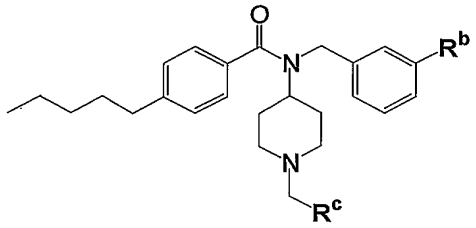
R^b	R^c	Data
		Example 122 LC-MS: tR = 0.93 ES+ = 503.51
		Example 123 LC-MS: tR = 0.92 ES+ = 489.51
		Example 124 LC-MS: tR = 0.94 ES+ = 517.49
		Example 125 LC-MS: tR = 1.03 ES+ = 501.50
		Example 126 LC-MS: tR = 1.04 ES+ = 515.50

Chart 19:



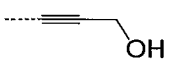
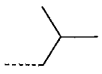
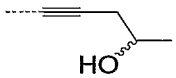
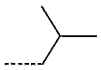
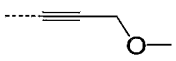
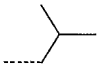
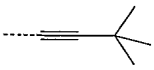
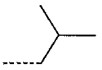
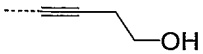
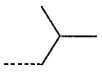
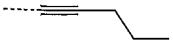
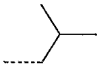
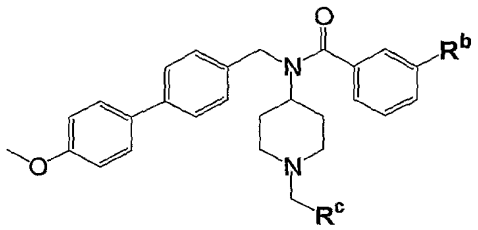
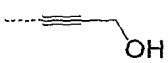
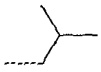
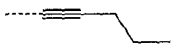
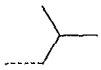
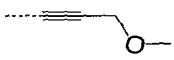
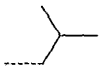
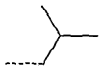
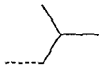
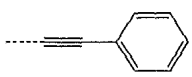
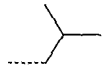
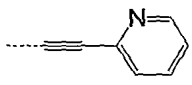
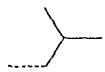
R^b	R^c	Data
		Example 127 LC-MS: tR = 0.92 ES+ = 489.48
		Example 128 LC-MS: tR = 0.94 ES+ = 517.48
		Example 129 LC-MS: tR = 0.98 ES+ = 503.49
		Example 130 LC-MS: tR = 1.04 ES+ = 515.50
		Example 131 LC-MS: tR = 0.93 ES+ = 503.49
		Example 132 LC-MS: tR = 1.03 ES+ = 501.51

Chart 20:

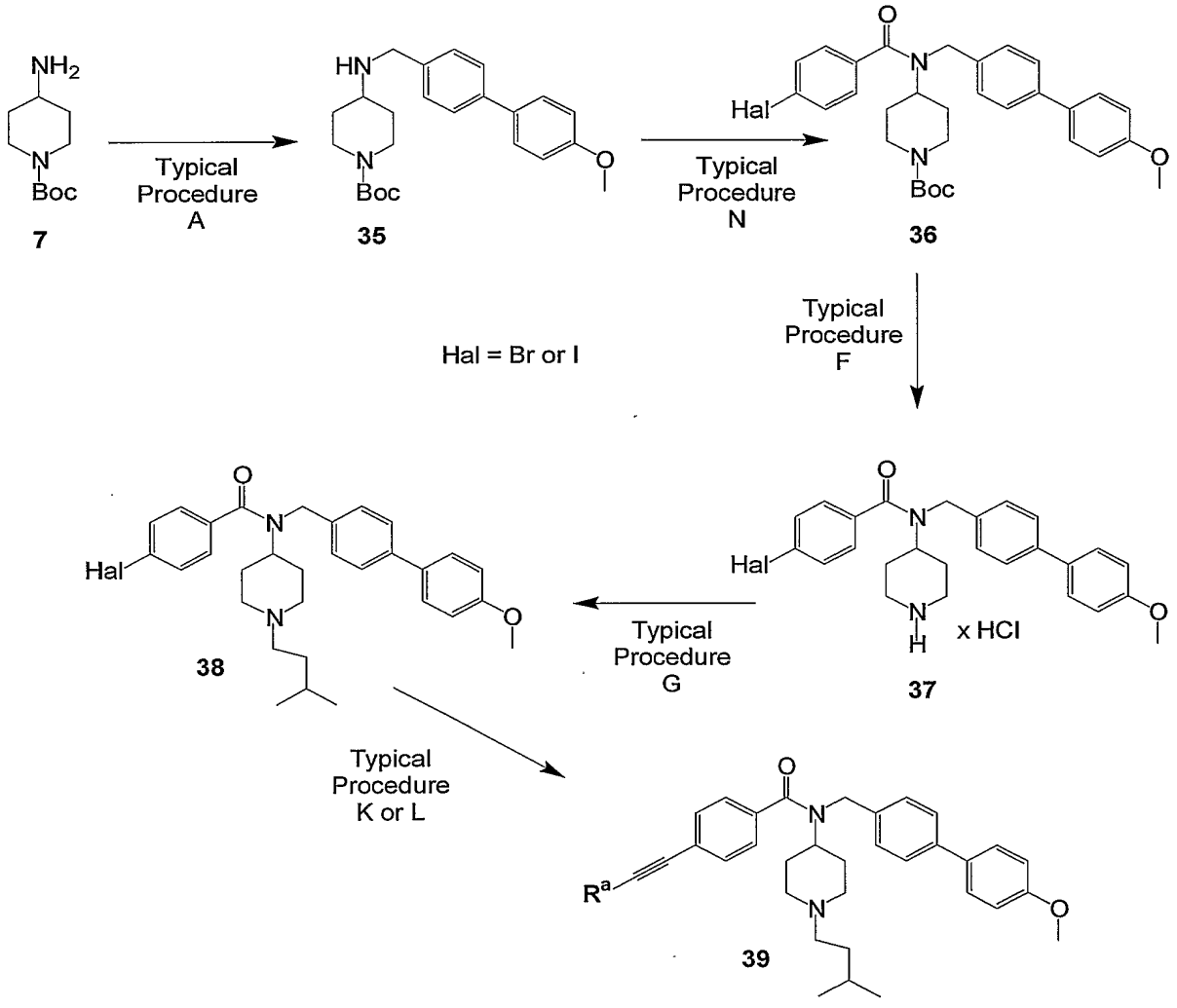


R^b	R^c	Data
		Example 133 LC-MS: tR = 0.87 ES+ = 525.27
		Example 134 LC-MS: tR = 0.99 ES+ = 537.30
		Example 135 LC-MS: tR = 0.93 ES+ = 539.29
		Example 136 LC-MS: tR = 1.00 ES+ = 551.30
		Example 137 LC-MS: tR = 1.00 ES+ = 551.28
		Example 138 LC-MS: tR = 0.99 ES+ = 571.26
		Example 139 LC-MS: tR = 0.91 ES+ = 572.24

Example 70 and 71 were prepared according to the Typical Procedures described on pages 35-39. Example 71 was subsequently used in *Suzuki*-reactions with aryl-boronic acids according to Typical Procedure H) (p. 38) to prepare Examples 72, 73 and 74.

Examples depicted in *Chart 16* were prepared as described in **Scheme 4**:

Scheme 4:

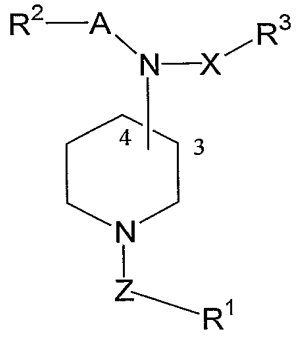


Examples depicted in *Charts 17 to 20* were prepared according to the synthetic pathway described in **Scheme 4** by changing certain starting materials in order to obtain the structural variations depicted in *Charts 17 to 20*.

5

Claims:

1. Pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders comprising substituted piperidines of the **general formula I**, wherein the substituent is attached either to position 3 or position 4 of the central piperidine-ring:



General Formula I

wherein

R^1 represents lower alkyl; lower alkenyl-lower alkyl; lower alkynyl-lower alkyl; cycloalkyl; cycloalkenyl-lower alkyl; heterocyclyl; aryl; heteroaryl;

R^2 represents cycloalkyl; cycloalkenyl; heterocyclyl; aryl; heteroaryl;

R^3 represents lower alkyl; cycloalkyl; cycloalkenyl; heterocyclyl; aryl; heteroaryl;

A represents $-(CH_2)_m-$;

X represents $-(CH_2)_n-CH_2-(CH_2)_j-$; $-(C=O)-(CH_2)_p-$; $-(C=O)-(CH_2)_p-NH-(CH_2)_q-$; $-(C=O)-(CH_2)_f-O-(CH_2)_p-$; $-(C=O)-(CH=CH)-$; $-(SO_2)-(CH_2)_p-$; $-(SO_2)-NH-(CH_2)_p-$; $-(SO_2)-(CH=CH)-$;

Z represents a bond; $-((CH_2)_n-CH_2-(CH_2)_j)-$; $-((CH_2)-(CH=CH))-$; $-(CH_2)_g-NH-(CO)-$; $-(CH_2)_g-NH-(CO)-O-$; $-(CH_2)_g-NH-(CO)-NH-$; $-(CH_2)_g-O-(CH_2)_m-$;

n and **j** represent the whole numbers 0, 1 or 2 and may be the same or different;

m represents the whole numbers 1, 2 or 3;

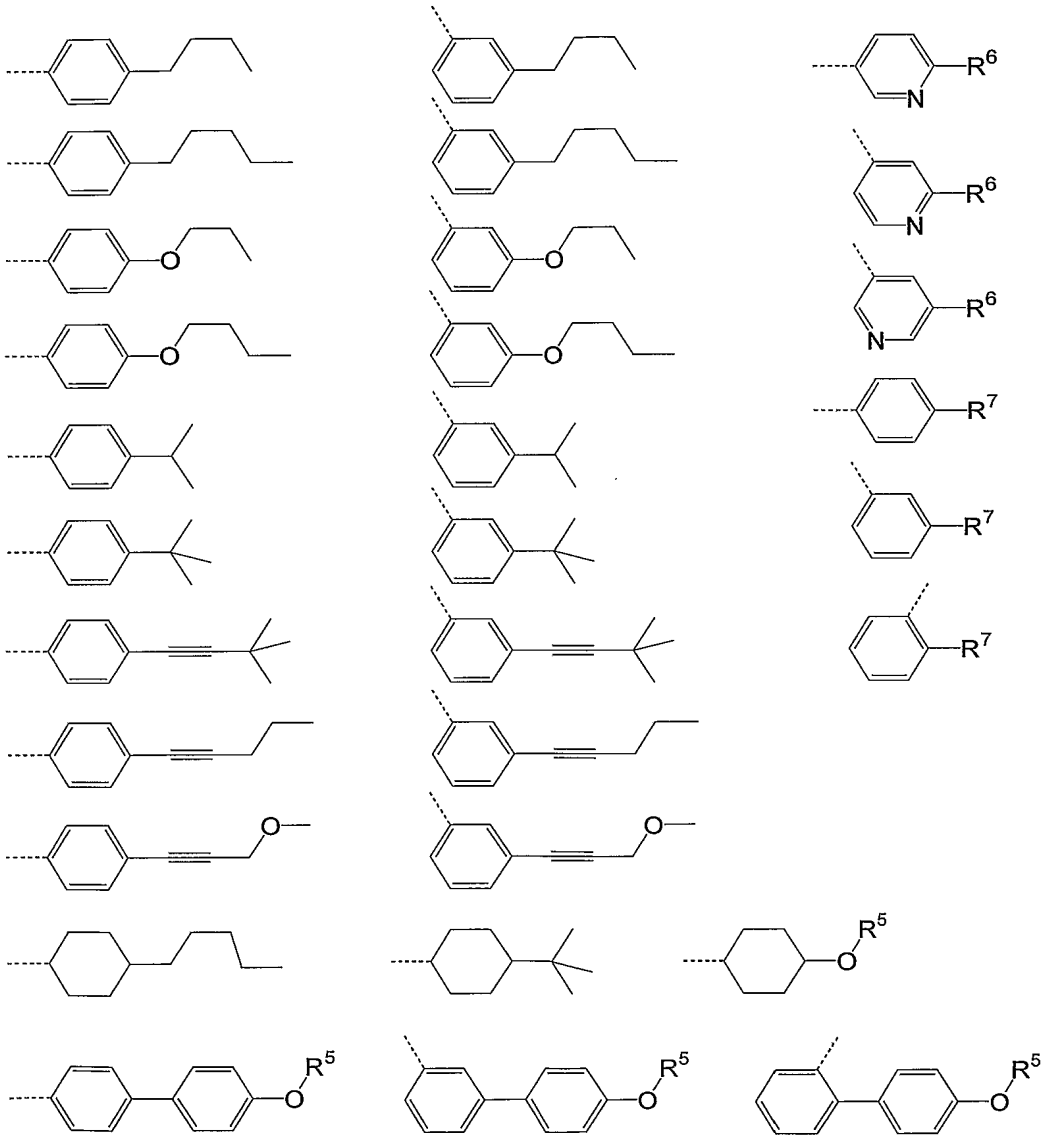
k, p and **q** represent the whole numbers 0, 1, 2, 3 or 4 and may be the same or different;

f represents the whole numbers 1, 2, 3 or 4;

g represents the whole numbers 2, 3 or 4;

pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, the meso-form, cis- and trans-isomers of carbon-carbon double bonds, pharmaceutically acceptable salts thereof, and inert carrier material.

2. Pharmaceutical compositions according to claim 1 comprising compounds of the **general formula I** wherein R^1, **A**, **X** and **Z** are as defined in **general formula I** above and the following structural formulae represent R^2 and R^3 whereby R^2 and R^3 may be the same or different:



wherein

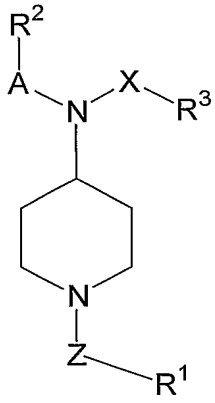
R^5 represents lower alkyl; hydroxy-lower alkyl; aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; heterocyclyl; heterocyclyl-lower alkyl; cycloalkyl; cycloalkyl-lower alkyl;

R^6 represents lower alkyl; lower alkynyl; aryl; heteroaryl; heterocyclyl; aryl-amino; heteroaryl-amino; cycloalkyl-amino; aryl-lower alkyl-amino; heteroaryl-lower alkyl-amino; heterocyclyl-lower alkyl-amino; cycloalkyl-lower alkyl amino; aryloxy; heteroaryloxy; cyloalkyloxy; aryl-lower alkyloxy; heteroaryl-lower alkyloxy; heterocyclyl-lower alkyloxy; cycloalkyl-lower alkyloxy;

R^7 represents aryl; heteroaryl; heterocyclyl; cycloalkyl; aryl-amino; heteroaryl-amino; cycloalkyl-amino; aryl-lower alkyl-amino; heteroaryl-lower alkyl-amino; heterocyclyl-lower alkyl-amino; cycloalkyl-lower alkyl amino; aryl-oxy; heteroaryl-oxy; aryl-lower alkyl-oxy; heteroaryl-lower alkyl-oxy;

pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, the meso-form, cis- and trans-isomers of carbon-carbon double bonds, pharmaceutically acceptable salts thereof, and inert carrier material.

3. Pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders comprising compounds of the **formula II**:



Formula II

wherein

R^1, R^2, R^3, X, Z and **A** are as defined in **general formula I** above

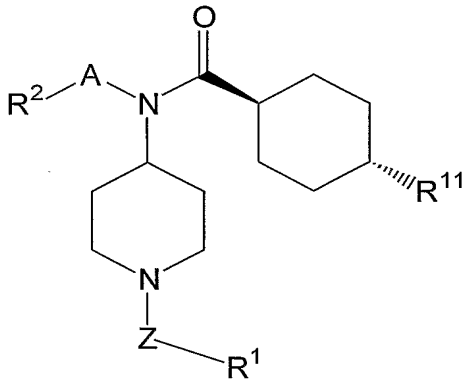
pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, the meso-form, cis- and trans-isomers of carbon-carbon double bonds, pharmaceutically acceptable salts thereof, and inert carrier material.

4. Pharmaceutical compositions according to claim 3 for treatment, prevention or delaying the onset of central nervous system disorders comprising compounds of the **formula II** given in claim 3, wherein **R^1**, **R^2**, **R^3**, **Z** and **A** are as defined in **general formula I** above and wherein **X** represents -(C=O)-NH-$(CH_2)_q$)- and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, the meso-form, cis- and trans-isomers of carbon-carbon double bonds, pharmaceutically acceptable salts thereof, and inert carrier material.

5. Pharmaceutical compositions according to claim 3 for treatment, prevention or delaying the onset of central nervous system disorders comprising compounds of the **formula II** given in claim 3, wherein $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, **Z** and **A** are as defined in **general formula I** above and wherein **X** represents $-(C=O)-(CH_2)_q-$ and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, the meso-form, cis- and trans-isomers of carbon-carbon double bonds, pharmaceutically acceptable salts thereof, and inert carrier material.

6. Pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders comprising compounds of the **formula III**:

Formula III



wherein

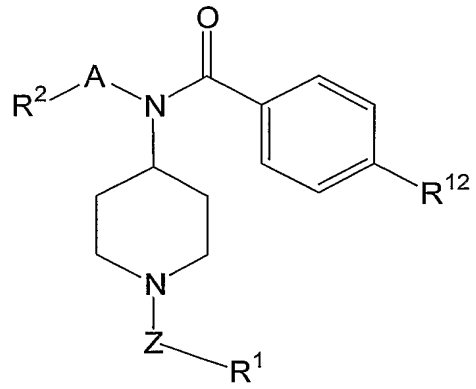
$\mathbf{R^1}$, $\mathbf{R^2}$, **Z** and **A** are as defined in **general formula I** above

$\mathbf{R^{11}}$ represents lower alkyl; lower alkyloxy; cycloalkyl; cycloalkyl-lower alkyloxy;

pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, the meso-form, cis- and trans-isomers of carbon-carbon double bonds, pharmaceutically acceptable salts thereof, and inert carrier material.

7. Pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders comprising compounds of the **formula IV**:

Formula IV



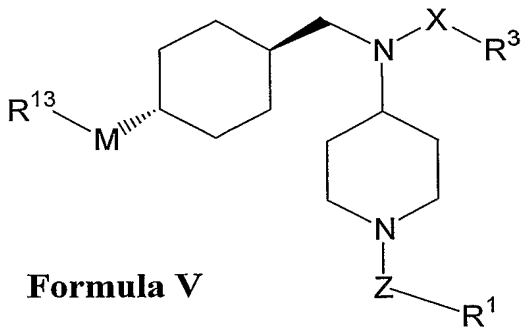
wherein

R^1, R^2 A and **Z** are as defined in **general formula I** above, and wherein

R^{12} represents lower alkyl; lower alkyloxy; lower alkyloxy-lower alkyloxy; aryl; heteroaryl; heterocyclyl;

pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, the meso-form, cis- and trans-isomers of carbon-carbon double bonds, pharmaceutically acceptable salts thereof, and inert carrier material.

8. Pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders comprising compounds of the **formula V**:



Formula V

wherein

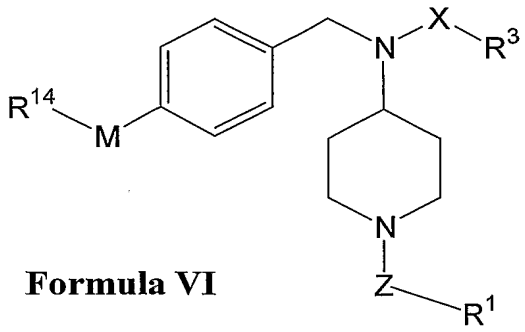
R^1, R^3, X and **Z** are as defined in **general formula I** above and

M represents -O-; -CH_2-;

R^{13} represents hydrogen; lower alkyl; lower alkenyl; lower alkynyl; cycloalkyl; cycloalkyl-lower alkyl; aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl;

pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, the meso-form, cis- and trans-isomers of carbon-carbon double bonds, pharmaceutically acceptable salts thereof, and inert carrier material.

9. Pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders comprising compounds of the **formula VI:**



Formula VI

wherein

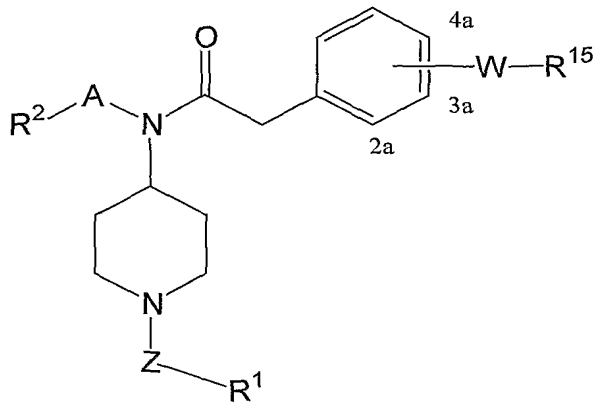
R^1, R^3, X, and **Z** are as defined in **general formula I**

M represents -O-; -CH_2-; or can be absent;

R^{14} represents hydrogen; lower alkyl; aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; cycloalkyl; cycloalkyl-lower alkyl; and in case **M** is absent, **R^{14}** can also represent heterocyclyl;

pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, the meso-form, cis- and trans-isomers of carbon-carbon double bonds, pharmaceutically acceptable salts thereof, and inert carrier material.

10. Pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders comprising compounds of the **formula VII**:



Formula VII

wherein

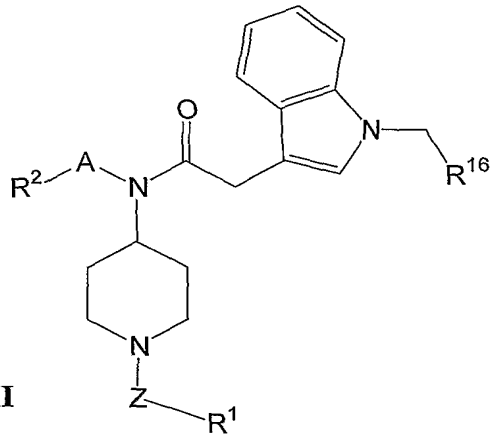
R^1, R^2, A and **Z** are as defined in **general formula I** above

R^{15} represents hydrogen; lower alkyl; lower alkenyl; lower alkynyl; cycloalkyl; cycloalkyl-lower alkyl; aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; and in case **W** represents a bond, **R^{15}** can also represent heterocyclyl; cyano; trifluoromethyl; trifluoromethoxy;

W represents a bond; -O-; -NH-; -N(R^{11})-; whereby in the group -N(R^{11})- the substituent **R^{11}** is as defined in formula III above, and **W** may be attached to the benzene-ring either in position 2a or 3a or 4a;

pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, the meso-form, cis- and trans-isomers of carbon-carbon double bonds, pharmaceutically acceptable salts thereof, and inert carrier material.

11. Pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders comprising compounds of the **formula VIII**:



Formula VIII

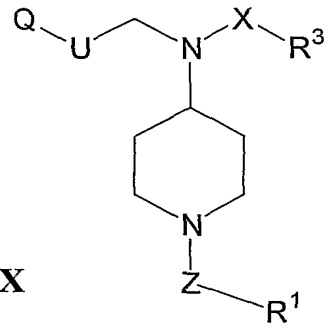
wherein

R^1, R^2, A and **Z** are as defined in **general formula I** above

R^{16} represents lower alkyl; lower alkenyl; lower alkynyl; cycloalkyl; cycloalkyl-lower alkyl; aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; heterocyclyl-lower alkyl;

pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, the meso-form, cis- and trans-isomers of carbon-carbon double bonds, pharmaceutically acceptable salts thereof, and inert carrier material.

12. Pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders comprising compounds of the **formula IX**:



Formula IX

wherein

R^1, R^3, **X** and **Z** are as defined in **general formula I** above

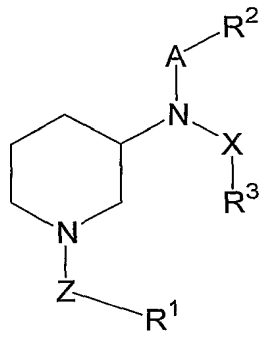
U represents aryl; heteroaryl;

Q represents aryl; heteroaryl; cycloalkyl; heterocyclyl; alkynyl;

pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, the meso-form, cis- and trans-isomers of carbon-carbon double bonds, pharmaceutically acceptable salts thereof, and inert carrier material.

13. Novel compounds of the **formula XI**:

Formula XI



wherein

R^1, R^2, R^3, X, Z and **A** are as defined in **general formula I** above

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

14. Novel compounds according to **formula XI** in claim 13, wherein **R^1, R^2, R^3, Z** and **A** are as defined in **general formula I** above and wherein **X** represents $-((C=O)-(CH_2)_q)-$ and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

15. Novel compounds according to **formula XI** in claim 13, wherein **R^1, R^2, R^3, Z** and **A** are as defined in **general formula I** above and wherein **X** represents $-((C=O)-NH-(CH_2)_q)-$ and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

16. Pharmaceutical compositions for treatment, prevention or delaying the onset of central nervous system disorders comprising compounds according to any one of the claims 1 to 15.

17. Pharmaceutical compositions containing one or more compounds as claimed in any of the claims 1 to 15 and any inert excipients.

18. Pharmaceutical compositions containing one or more compounds as claimed in any of the claims 1 to 15 and any inert excipients in combination with one or more therapeutic agents selected from the group consisting of anti-oxidants, anti-inflammatory agents, γ-secretase inhibitors, statins, LDL lowering agents, an amyloid-β-peptide derivative and an anti-amyloid-β-peptide antibody, steroidhormones, antidepressant and antipsychotic agents, neurotrophic factors, metal ion chelators, insulin-sensitizers and acetylcholine esterase inhibitors.

19. Pharmaceutical compositions according to any of the claims 16 to 18 for treatment, prevention or delaying the onset or the progression of diseases requiring the inhibition of aspartic proteases.

20. Pharmaceutical compositions according to any of the claims 16 to 18 for treatment, prevention or delaying the onset or the progression of disorders associated with the role of β-secretase (BACE1) and which require selective inhibition of β-secretase (BACE1).

21. Pharmaceutical compositions according to any of the claims 16 to 18 for treatment, prevention or delaying the onset or the progression of diseases and disorders selected from the group consisting of Alzheimer's disease, mild cognitive impairment (MCI), Down's syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch-type, cerebral amyloid angiopathy, other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration or diffuse Lewy body type of Alzheimer's disease and the like.

22. Pharmaceutical compositions according to any of the claims 16 to 18 for treatment, prevention or delaying the onset or progression of Alzheimer's disease.

23. Pharmaceutical compositions according to any of the claims 16 to 18 for treatment, prevention or delaying the onset or progression of mild cognitive impairment.

24. Pharmaceutical compositions according to any of the claims 16 to 18 for treatment, prevention or delaying the onset or progression of Down's syndrome.

25. Pharmaceutical compositions according to any of the claims 16 to 18 for treatment, prevention or delaying the onset or progression of cerebral hemorrhage with amyloidosis of the Dutch-type.

26. Pharmaceutical compositions according to any of the claims 16 to 18 for treatment, prevention or delaying the onset or progression of cerebral amyloid angiopathy.

27. Pharmaceutical compositions according to any of the claims 16 to 18 for treatment, prevention or delaying the onset or progression of degenerative dementias.

28. Pharmaceutical compositions according to any of the claims 16 to 18 for treatment, prevention or delaying the onset or progression of Lewy body type of Alzheimer's disease.

29. Pharmaceutical compositions according to any of the claims 16 to 18 for treatment, prevention or delaying the onset or progression of diseases characterized by deposites of amyloid-β-peptides in the brain.

30. A method for inhibiting β-secretase activity by exposing said β-secretase in vitro (isolated enzyme assay), in a cell, in an animal, or in humans to an effective inhibitory amount of a compound according to any of the claims 1 to 15 or a pharmaceutical composition according to any of the claims 16 to 18.

31. A method for inhibiting the production of amyloid-β-peptides (Aβ) in vitro (isolated enzyme assay), in a cell, in an animal, or in humans by administering an effective inhibitory

amount of a compound according to any of the claims 1 to 15 or a pharmaceutical composition according to any of the claims 16 to 18.

32. A method for inhibiting the production of amyloid-β–peptide plaques in an animal, or in humans by administering an effective inhibitory amount of a compound according to any of the claims 1 to 15 or a pharmaceutical composition according to any of the claims 16 to 18.

33. A process for the preparation of a pharmaceutical composition according to any of the claims 16 to 29, characterized by mixing one or more active ingredients according to any of the claims 1 to 15 with inert excipients in a manner known per se.

34. A process for the preparation of a pharmaceutical composition according to any of the claims 16 to 29, characterized by mixing one or more active ingredients according to any of the claims 1 to 15 with inert excipients and one or more additional active ingredients selected from the group consisting of anti-oxidants, anti-inflammatory agents, γ-secretase inhibitors, statins, LDL lowering agents, an amyloid-β-peptide derivative and an anti-amyloid-β-peptide antibody, steroidhormones, antidepressant and antipsychotic agents, neurotrophic factors, metal ion chelators, insulin-sensitizers and acetylcholine esterase inhibitors, in a manner known per se.

35. Use of at least one of the compounds of general formula I for the treatment, prevention or delaying the onset or progression of diseases.

36. Method of treating a patient suffering from central nervous system disorders by administering a pharmaceutical composition as claimed in any one of claims 16 to 29.

37. Method according to claim 36 by administering a pharmaceutical composition containing a compound as claimed in any one of claims 1 to 15 in a dose of 1 mg to 1000 mg.

38. Method according to claim 36 by administering a pharmaceutical composition containing a compound as claimed in any one of claims 1 to 15 in a dose of 2 mg to 500 mg.

39. Method according to claim 36 by administering a pharmaceutical composition containing a compound as claimed in any one of claims 1 to 15 in a dose of 5 mg to 250 mg.